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Defining predictive models of the variation in esophageal cancer incidence

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The longer you can look back, the farther you can look forward.

Winston Churchill

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ABSTRACT

Cancer prevention and control programs rely on mortality data, from vital statistics, and incidence data, provided by population-based cancer registries. In this context, prediction models are valuable sources of information, not only to provide future estimates of the burden of cancer, but also to suppress the lag between data collection and their publication.

Esophageal cancer is one of the most lethal cancers, and its public health relevance has increased in the last decades due to the steeply increasing incidence trends observed in Western countries. Esophageal cancer has two major histological types, squamous cell carcinoma (ESCC) and adenocarcinoma (EAC), which present various patterns of incidence trends, reflecting differences in their etiologies. Despite the extensive knowledge on the main risk factors for esophageal cancer, their joint contribution for the trends in the burden of disease associated with esophageal cancer has not been formally assessed. Therefore, we aimed to develop a model able to describe and predict the variation in its incidence at a population level, taking into account the variation in the exposure to the main modifiable risk factors. Five studies (Papers I-V) were performed to accomplish the specific objectives necessary for the development of the model, which are mentioned below:

Paper I – Patterns and trends in esophageal cancer mortality and incidence in Europe (1980-2011) and predictions to 2015.

Paper II – Cancer incidence predictions in the North of Portugal: keeping population-based cancer registration up to date.

Paper III – Trends in gastric and esophageal cancers incidence in Northern Portugal (1994-2009), by subsite and histology, and predictions for 2015.

Paper IV – Modifiable factors and esophageal cancer: a systematic review of published meta-analyses.

Paper V – An explanatory and predictive model of the variation in esophageal cancer incidence, based on changes in the exposure to risk factors.

1. To describe the trends in esophageal cancer incidence, overall and by histological type, in different countries, including Portugal (Papers I-III);

Cancer incidence data in Europe (Paper I) were obtained, by sex and age group, from Cancer Incidence in Five Continents (CI5) databases and analyzed by histological type. Annual data for the period 1980–2002 were derived from the CI5-plus database. Grouped data referring to the period 1998–2002 were retrieved from CI5-IX to describe the geographical distribution of esophageal cancer histological types across Europe. For countries with more than one cancer registry, data were aggregated to ensure the highest geographic coverage. In Northern Portugal (Papers II and III), data were retrieved from the North Region Cancer Registry (RORENO) for the period 1994-2009.

Among men, increasing EAC incidence trends were observed in most European countries, while ESCC trends have been decreasing or stabilizing over the last few decades. In Northern Europe, the increases in male EAC trends were among the steepest observed, and EAC is now more frequent than ESCC. In central and southern Europe, smaller rises in EAC were observed and ESCC remains the predominant histological type among men. Trends were less stable among women, and ESCC was the predominant subtype in all settings. In Northern Portugal, men presented an upward trend for ESCC and a decline in EAC, while women had opposite trends; the proportion of cases of unspecified histological type was below 10%.

2. To summarize the evidence on the exposure to the different risk factors of esophageal cancer in Northern Portugal over the past decades (Paper III);

A review of literature published up to 2014 was performed to evaluate the prevalence of tobacco smoking, alcohol drinking, overweight and obesity, *H. pylori* infection, and fruit and vegetable consumption in Northern Portugal. For tobacco smoking, overweight/obesity and *H. pylori* infection, previously published systematic reviews of Portuguese studies were used as the primary source of published reports. For the other risk factors, data were collected from national health surveys and population-based studies conducted in the region.

Among adults, the prevalence of smoking decreased for men and increased among women. The opposite was observed for alcohol drinking. The prevalence of overweight and obesity increased for both sexes, among children and among adults. The prevalence of *H. pylori* infection increased with age, but no clear trend was observed over time. The prevalence of daily consumption of fruit and vegetable showed relatively stable trends, with the consumption of fruits being higher than that of vegetables among adults.

3. To summarize the current scientific knowledge on modifiable risk factors for esophageal cancer, by histological type, through a systematic review of published meta-analyses (Paper IV);

PubMed and ISI Web of Knowledge were searched up to September 2015 to identify meta-analyses addressing the association between the main modifiable risk factors and esophageal cancer. Each meta-analysis was attributed a quality score, ranging from 0 to 11, based on the AMSTAR tool.

We identified 95 meta-analyses, of which 47 focused on ESCC and 46 on EAC; half of the studies had a quality score of 7 or higher. Dose-response effects were found for ESCC regarding alcohol consumption and tobacco smoking, and cessation of either exposure significantly reduces the risk of ESCC. No significant associations were found between alcohol consumption and EAC. EAC risk was found decreasing by 50% in the presence of *H. pylori* infection, but it increased gradually with the increasing frequency and duration of GERD symptoms. A dose-response effect of BMI was found for EAC, while it was reported decreasing the risk of ESCC. Dietary aspects were extensively assessed in numerous meta-analyses. Increments of 100 g/day in fruit and vegetable intake were found decreasing ESCC risk by approximately 40% and 16%, respectively; for EAC, corresponding values were of 13% and 9%. Dose-response effects were also reported for red and processed meat, which increase the risk of both subtypes.

4. To estimate the contribution of the variation in the exposure to the main risk factors for esophageal cancer to changes in its incidence rates between 1995 and 2005, in Northern Portugal and in selected countries (Paper V).

We adapted an existing model (IMPACT) to calculate the expected variation in the number of esophageal cancer cases, between 1995 and 2005, due to changes in exposures to risk factors, taking into account the corresponding lag times. Analyses were based on country-specific data of cancer incidence (retrieved from CI5 and RORENO) and exposures to risk factors (collected from WHO databases, national health and nutrition surveys, and literature searches). Monte Carlo simulation methods were used to compute 95% credibility intervals.

Absolute deviations between the number of cases predicted and those observed in 2005 ranged between 1.8% in Japan and 23.6% in the United Kingdom (UK) among men; 0.0% in Japan and 18.0% in Australia among women. In Italy and Japan, deviations did not exceed 3%. The UK registered the worst model performance. The contribution of each risk factor to the observed changes in esophageal cancer incidence varied widely between countries, sexes and cancer subtypes. The major contributors to trends in esophageal cancer incidence were changes in fruit and red meat intake, and body mass index. For nearly half of the sex- and histological type-specific predictions performed, the credibility intervals included the observed number of cases in 2005.

In conclusion, this thesis adds to previous research on this topic a framework for analysis of the contribution of the variation in the exposure to different factors known to be associated with esophageal cancer, as well as for long-term predictions of ESCC and EAC at a population level. The results obtained in this work show the potential of this model for the planning of interventions and to define cancer control policies, but future studies, taking into account a wider period of time between exposure assessments, while also using more accurate estimates of the variation in the exposure to the risk factors, are expected to improve the accuracy of predictions.

RESUMO

Os programas de prevenção e controlo de cancro dependem de dados de mortalidade, provenientes de estatísticas oficais, e de dados de incidência, fornecidos por registos oncológicos de base populacional. Neste contexto, os modelos de projeção são uma fonte valiosa de informação, não só para fornecer estimativas futuras da incidência de cancro, mas também para colmatar o tempo existente entre a colheita de dados e a sua publicação.

O cancro do esófago é um dos cancros mais letais, e a sua relevância ao nível da saúde pública tem aumentado nas últimas décadas devido às tendências de aumento de incidência observadas nos países ocidentais. O cancro do esófago apresenta dois tipos histológicos principais, o carcinoma de células escamosas (CCEE) e o adenocarcinoma (ACE), que apresentam padrões de tendências de incidência distintos que refletem as diferenças das suas etiologias. Apesar do amplo conhecimento sobre os principais fatores de risco para o cancro do esófago, a sua contribuição conjunta para as tendências da carga da doença associada ao cancro do esófago não foi formalmente avaliada. Assim, procurou-se desenvolver um modelo capaz de descrever e prever a variação da incidência de cancro do esófago a nível populacional, tendo em conta a variação na exposição aos principais factores de risco modificáveis. Foram realizados cinco estudos (Artigos I-V) para responder aos objetivos específicos necessários ao desenvolvimento do modelo, descritos abaixo:

Artigo I – Patterns and trends in esophageal cancer mortality and incidence in Europe (1980-2011) and predictions to 2015.

Artigo II – Cancer incidence predictions in the North of Portugal: keeping population-based cancer registration up to date.

Artigo III – Trends in gastric and esophageal cancers incidence in Northern Portugal (1994-2009), by subsite and histology, and predictions for 2015.

Artigo IV – Modifiable factors and esophageal cancer: a systematic review of published meta-analyses.

Artigo V – An explanatory and predictive model of the variation in esophageal cancer incidence, based on changes in the exposure to risk factors.

1. Descrever as tendências na incidência de cancro do esófago, no global e por tipo histológico, em diferentes países, incluindo Portugal (Artigos I-III);

Foram obtidos dados de incidência na Europa (Artigo I), por sexo e grupo etário, usando as bases de dados das publicações Cancer Incidence in Five Continents (CI5), que foram analisados por tipo histológico. A base de dados CI5-plus foi usada para a recolha de dados anuais para o período 1980-2002. Foram também recolhidos dados agregados relativos ao período 1998-2002, usando a publicação CI5-IX, para descrever a distribuição geográfica dos tipos histológicos de cancro do esófago na Europa. Para os países com mais do que um registo oncológico, os dados foram agrupados para garantir a maior cobertura geográfica possível. No Norte de Portugal (Artigos II e III), os dados foram obtidos do Registo Oncológico Regional do Norte (RORENO), para o período 1994-2009.

Nos homens, foram observadas tendências crescentes da incidência de ACE na maioria dos países europeus, enquanto as tendências do CCEE têm vindo a diminuir ou estabilizar ao longo das últimas décadas. No Norte da Europa, os aumentos nas tendências de ACE no sexo masculino foram dos mais marcados, e o ACE é atualmente mais frequente do que o CCEE. Na Europa Central e do Sul, foram observados aumentos menos marcados para o ACE, e o CCEE permanece o tipo histológico predominante no sexo masculino. As tendências foram menos estáveis entre as mulheres, sendo o CCEE o subtipo predominante em todos países. No Norte de Portugal, os homens apresentaram uma tendência crescente para o CCEE e decrescente para o ACE, enquanto que as mulheres apresentaram tendências opostas; a proporção de casos com tipo histológico não especificado foi inferior a 10%.

2. Sumariar a evidência sobre a exposição a diferentes fatores de risco de cancro do esófago no Norte de Portugal nas últimas décadas (Artigo III);

Foi realizada uma revisão da literatura publicada até 2014 para avaliar a prevalência de consumo de tabaco, consumo de álcool, excesso de peso e obesidade, infecção por *H. pylori*, e consumo de frutas e vegetais no Norte de Portugal. Para o consumo de tabaco, excesso de peso e obesidade e infecção por *H. pylori*, foram usadas revisões sistemáticas de estudos portugueses previamente publicadas como fonte primária de estudos elegíveis. Para os outros fatores de risco, os dados foram recolhidos a partir dos inquéritos nacionais de saúde e estudos de base populacional realizados na região.

Nos adultos, a prevalência de consumo de tabaco diminuiu nos homens e aumentou nas mulheres. O oposto foi observado para a prevalência de consumo de álcool. A prevalência de excesso de peso e obesidade aumentou para ambos os sexos, nas crianças e nos adultos. A prevalência de infecção por *H. pylori* aumentou com a idade, mas foi detetada uma tendência clara ao longo do tempo. As prevalências de consumo diário de frutas e vegetais apresentaram uma tendência relativamente estável, sendo o consumo de frutas superior ao dos vegetais entre os adultos.

3. Sumariar o conhecimento científico atual sobre os fatores de risco modificáveis do cancro do esófago, por tipo histológico, através de uma revisão sistemática de meta-análises (Artigo IV);

Foram utilizadas as bases da PubMed e ISI Web of Knowledge para identificar meta-análises publicadas até setembro de 2015, que avaliassem a associação entre os principais fatores de risco modificáveis e o cancro do esófago. Foi atribuído um score de qualidade a cada meta-análise, entre 0 e 11, com base na ferramenta AMSTAR.

Foram identificadas 95 meta-análises, das quais 47 avaliaram o CCEE e 46 o ACE; metade dos estudos tiveram um score de qualidade igual ou superior a 7. Foram encontrados efeitos dose-resposta para o CCEE relativamente ao consumo de álcool e de tabaco, e a cessação de qualquer uma dessas exposições reduzia significativamente o risco de ESCC. Não foram encontradas associações significativas entre o consumo de álcool e o ACE. Foi detetada uma diminuição de 50% no risco de ACE na presença de infecção por *H. pylori*, mas um aumento gradual com a frequência e duração dos sintomas de refluxo gastroesofágico. Foi descrito um efeito dose-resposta do índice de massa corporal em relação ao aumento do risco de ACE e, simultaneamente, de diminuição do risco de CCEE. Os aspetos ligados à alimentação foram amplamente avaliados em várias meta-análises. Foi estimado que um aumento de 100 g/dia na ingestão de frutas e vegetais diminuia o risco de CCEE em 40% e 16%, respetivamente; para o ACE, os valores correspondentes foram de 13% e 9%. Foram também descritos efeitos dose-resposta de aumento do risco para ambos os subtipos em relação a carne vermelha e carne processada.

4. Estimar a contribuição das mudanças na exposição aos principais fatores de risco para o cancro do esófago para as variações encontradas nas taxas de incidência entre 1995 e 2005, no Norte de Portugal e em países seleccionados (Artigo V).

Foi adaptado um modelo previamente existente (IMPACT) para calcular a variação esperada no número de casos de cancro de esófago, entre 1995 e 2005, devida a mudanças na exposição a fatores de risco, tendo em conta o tempo que decorre entre a exposição e o *outcome*. A análise estatística foi baseada em dados específicos de cada país relativos à incidência de cancro (recolhidos do CI5 e do RORENO) e à exposição a fatores de risco (recolhidos de bases de dados da Organização Mundial de Saúde, inquéritos nacionais de saúde e de nutrição e pesquisas bibliográficas). Foram usados métodos de simulação de Monte Carlo para calcular intervalos de credibilidade a 95%.

Os desvios, em módulo, entre o número de casos previsto e o observado em 2015 variaram entre 1,8% no Japão e 23,6% no Reino Unido no sexo masculino e entre 0,0% no Japão e 18,0% na Austrália no sexo feminino. Na Itália e no Japão, os desvios não excederam os 3%. O Reino Unido registrou o pior desempenho do modelo. A contribuição de cada fator de risco para as

alterações observadas na incidência de cancro do esófago variaram amplamente entre países, sexos e subtipos histológicos. Os fatores mais determinantes para as variações na incidência de cancro do esófago foram alterações no consumo de frutas e de carne vermelha, e variações no índice de massa corporal. Os intervalos de credibilidade incluiram o número de casos observados para quase metade das estimativas efetuadas por tipo histológico e por sexo.

Em conclusão, esta tese apresenta uma metodologia para a análise da contribuição da variação da exposição a diferentes fatores de risco na variação da incidência de cancro do esófago, bem como para projeções a longo prazo para o CCEE e o ACE a nível populacional. Os resultados obtidos neste trabalho mostram o potencial deste modelo para o planeamento de intervenções e definição de políticas de controlo do cancro, mas espera-se que estudos futuros, efetuados para previsões a mais longo prazo, usando simultaneamente estimativas mais precisas da variação na exposição aos factores de risco, possam melhorar a validade das estimativas.

INTRODUCTION

Prediction models are a valuable source of information for policies aiming to control and reduce the burden of disease in a given population. Since public health interventions heavily rely on adequate data supporting their need and cost-effectiveness, the collection of population-based information, along with scientific knowledge on the causes of a disease and their underlying mechanisms are of major importance. In the context of cancer research, several prediction methods have been developed, with a wide range of complexity regarding both the mathematical models involved and the level of detail of the data required.

As cancer is a worldwide public health issue, many countries have national programs specifically targeting this disease. For their definition and evaluation, cancer prevention and control programs often rely on mortality data, from vital statistics, and incidence data, provided by regional or national population-based cancer registries, after the collection and treatment of the information on cancer cases occurring in their coverage area. Although there are no formal guidelines for the timeliness of cancer registry data, several North American agencies (particularly those providing funding via contracts) have set a two- to three-year standard for relevant registries, namely the Surveillance, Epidemiology, and End Results (SEER) Program, Centers for Disease Control and Prevention/National Program of Cancer Registries, and the North American Association of Central Cancer Registries[1]. However, worldwide there is a large heterogeneity between cancer registries regarding the most recent year of incidence data available[2], which enhances the usefulness of prediction models, not only for long-term predictions of the burden of cancer, but also to suppress the lag between data collection and their publications.

Globally, cancer incidence has been rising over time, mainly due to the increase in life expectancy, the aging of the population and changes in the exposure to risk factors[3]. However, cancers occurring in different anatomical sites present diverse etiologies, as well as different rates of improvement in early detection and treatment, which leads to various patterns of incidence and mortality trends. Esophageal cancer is one of the most lethal cancers, with five-year survival rates of 17% being reported in the United States of America (USA) and 12% in Europe[4, 5]. Furthermore, the public health relevance of this cancer has increased in the last decades due to the steeply increasing incidence trends observed in Western countries, which are usually considered to be of low-risk for esophageal cancer[6].

EPIDEMIOLOGY OF ESOPHAGEAL CANCER

PATHOLOGY AND NATURAL HISTORY

Esophageal cancer presents with two major histological types, squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). Sarcomas and small cell carcinomas rarely occur, comprising less than 1-2% of all esophageal cancer cases[4]. ESCC most often arises in the middle third of the esophagus, followed by the lower and the upper third, while EAC usually develops in the lower third. The etiology of the two subtypes appears to differ substantially, which translates into very diverse patterns regarding incidence rates and trends. Understanding the pathogenesis and biologic nature of their precursor lesions, which can be observed in the esophageal epithelium during neoplastic progression, is useful to avoid or treat esophageal malignancies.

Although precursor lesions of ESCC are not particularly well defined, transition models, especially in high-risk populations, have described inflammation in squamous epithelium to cause dysplasia, ultimately leading to *in situ* or invasive tumors[7, 8].

It is well accepted that EAC develops through a multistep transformation of the epithelium of the esophagus (Figure 1). Barrett's esophagus (BE), or columnar lined esophagus, is a premalignant condition that results from chronic gastroesophageal reflux (GERD) and predisposes to EAC. GERD occurs when the lower esophageal sphincter does not close properly, allowing acid to back up into the esophagus; when this reflux occurs frequently, it may lead to esophagitis, narrowing of the esophagus, bleeding, and dysphagia, which may cause BE; a greater duration and frequency of GERD symptoms, which include heartburn, regurgitation and dysphagia, have been found to further increase the risk of BE[9]. BE is usually diagnosed by biopsy, during upper gastrointestinal endoscopy for the assessment of GERD. Although some studies have suggested an upward trend in the population-based prevalence of BE, part of this increase likely reflects an increased detection through the wider use of upper gastrointestinal endoscopy in more recent years[10]. BE is characterized by the metaplastic replacement of the normal squamous epithelium of the lower esophagus by columnar epithelium, which may then progress through low- and high-grade dysplasia to the development of EAC[11].

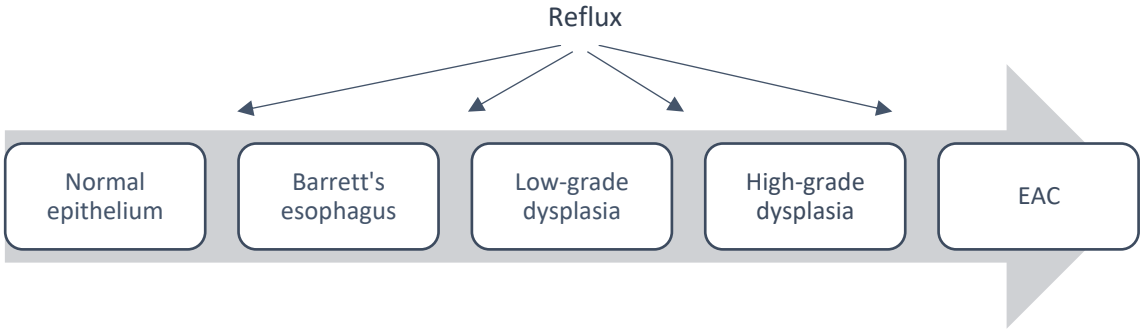

Figure 1. Neoplastic progression from normal esophageal epithelium to esophageal adenocarcinoma (EAC) (adapted from Wild[11]).

Dysplasia is considered to be present when there are architectural and cytological changes severe enough to suggest neoplastic transformation. The definition of low- or high-grade dysplasia is based on the magnitude of changes, which are especially relevant if they involve the mucosal surface[12].Progression from BE to high-grade dysplasia and from high-grade dysplasia to EAC has been estimated to lag 9-13 years and 3-4 years, respectively[13].

The risk of EAC in BE patients has been estimated to be 30- to 60-fold higher than in the general population, and 0.5% to 1% are expected to progress to EAC per year[14-16]. These imprecise estimates are due to the fact that most studies have followed a small number of individuals, for short periods of time, finding few incident EAC cases; some cohort studies have also included patients referred to a specialist center, which may have led to the inclusion of more cases of high-grade dysplasia than would be observed in the general population[17]. The length of the esophagus showing metaplastic changes also influences the risk of EAC, with individuals with long-segment BE (LSBE) (≥ 3 cm in length) being at higher risk than the ones with the more common short-segment BE (SSBE)[9]. A systematic review of studies published up to 2008 showed that GERD symptoms were not associated with SSBE, while increasing the odds of LSBE by five-fold[18]. This may contribute to explain the lower risk of EAC in SSBE patients. Other risk factors for BE include obesity, alcohol drinking and tobacco smoking, while a protective effect has been reported regarding *Helicobacter pylori* (*H. pylori*) infection[9].

Concomitantly to the metaplasia–dysplasia–adenocarcinoma sequence, several studies have showed the accumulation of genetic abnormalities in the transition from normal cells to malignant ones[19, 20]. Some of these genetic changes, namely variations in DNA ploidy, increased proliferation and alterations of the p53 gene, have been proposed as potentially helpful for screening and surveillance of patients with BE[12, 21]. However, to date none of the proposed biomarkers has been prospectively validated[9] and the most recent guidelines from the American Gastroenterological Association recommend against their usage for risk stratification of patients[22].

GEOGRAPHIC VARIATION

Esophageal cancer ranks as the eighth most common malignancy in the world and the sixth leading cause of death from cancer[6, 23]. However, the burden of esophageal cancer varies widely across geographical regions (Figure 2). According to the most recent estimates provided by the GLOBOCAN Project, esophageal cancer accounted for approximately 456 000 new cases, comprising 3.2% of all cancers (4.3% among men and 2.0% among women) and 400 000 deaths (6.0% of all cancer deaths among men and 3.4% among women) in 2012[23].

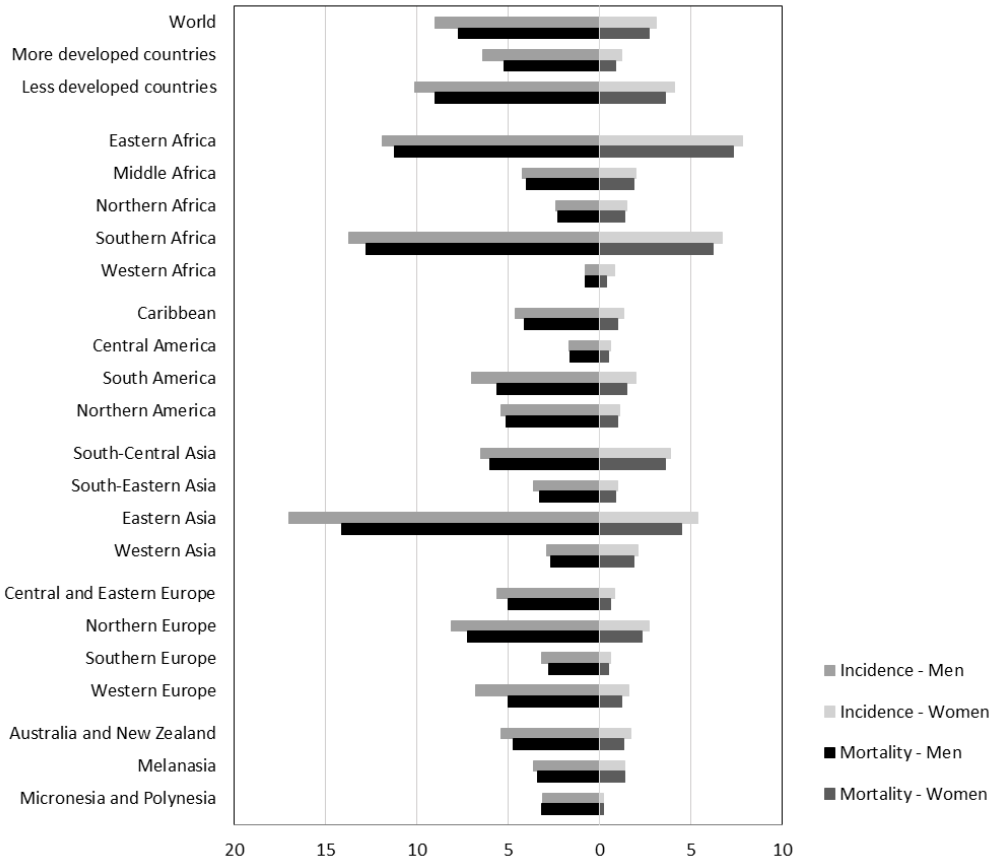

Figure 2. Worldwide age-standardized (World standard population) incidence and mortality rates per 100 000 of esophageal cancer in 2012 (source: Ferlay[23]).

In 2012, among men, the age-standardized (World standard population) incidence rates (ASIR) per 100 000 varied between 6.4 in more developed countries and 10.1 in less developed countries, while among women rates varied between 1.2 and 4.1[23]; the male/female ratio ranged between 1.0 in Western Africa and 15.5 in Micronesia and Polynesia. Approximately 80% of esophageal cancer cases occurred in less developed countries, with ASIR being 1.6 and 3.4 times higher than the ones observed in more developed countries, among men and women, respectively.

The geographical area commonly referred to as the "esophageal cancer belt," which extends from Northern Iran and Central Asia to Northern and Western China, has been described,

together with some areas of Southern Africa, as having the highest ASIR and age-standardized (World standard population) mortality rates (ASMR) worldwide[24]. In 2012, the countries with the highest ASIR were Malawi (24.2/100 000) and Turkmenistan (19.7/100 000), followed by Kenya and Mongolia (17.6/100 000)[23]. Among men, ASIR in Eastern Asia (17.0/100 000) were over 20-fold the ones estimated for Western Africa (0.8/100 000) and 10-fold the ones in Central America (1.7/100 000)[23]. Among women, the largest difference was observed between Eastern Africa (7.8/100 000), and Micronesia/Polynesia (0.2/100 000).

In the so-called low-risk settings, there are also relevant variations in incidence and mortality rates. In the USA, where esophageal cancer is the seventh leading cause of death from cancer, and an ASIR of 3.2 was estimated for 2012[23], some notably high ASIR have been described in coastal areas of Southern Carolina, especially among black men[25]. In Europe, the highest ASIR among men have been reported in the United Kingdom (UK) and the Netherlands, whereas the lowest were observed in Georgia; among women, the highest ASIR have also been detected in the UK, while the lowest were found in Greece, Macedonia and the Republic of Moldova[26]. The UK also presented the highest ASMR in Europe for both sexes, followed by the Netherlands among men and Ireland among women[26, 27]. In Portugal, where some of the highest ASMR in Europe have been observed among men[26], esophageal cancer was the tenth most common cancer in 2010, with an ASIR of 5.5 and 0.7 per 100 000, among men and women, respectively[28]. However, there was a wide geographical distribution of cases within the country, with the highest ASIR being observed in the Northern Region (6.5 and 0.8 among men and women, respectively) (Figure 3).

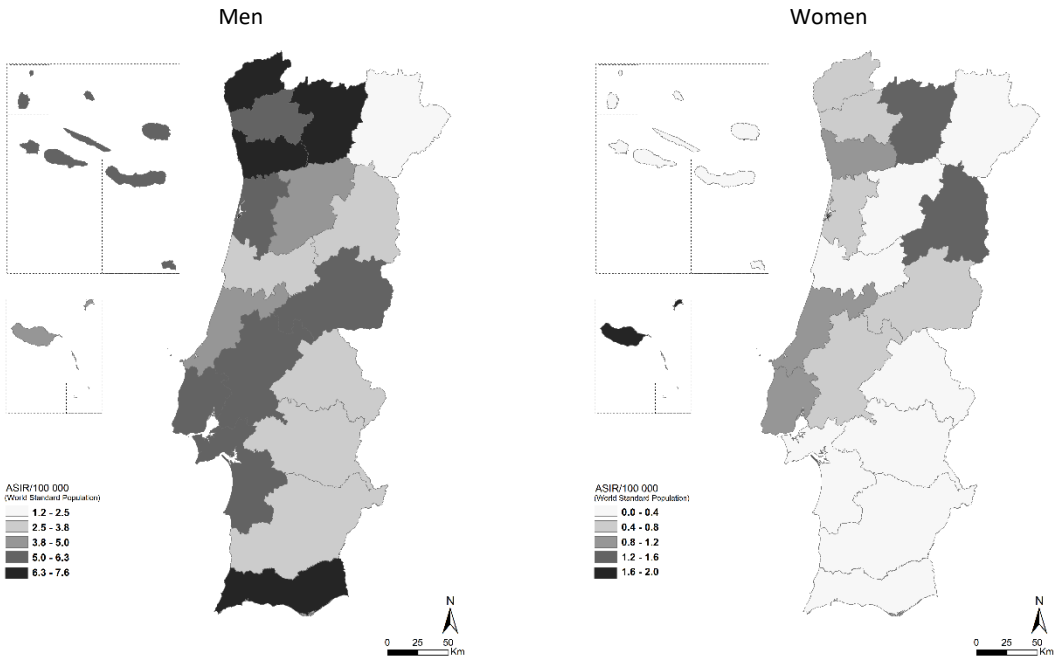

Figure 3. Geographic distribution of age-standardized (World standard population) incidence rates (ASIR) of esophageal cancer in Portugal, by sex (source: RORENO[28]).

In the high-risk areas for esophageal cancer, the predominant histological type is ESCC, which comprises approximately 90% of all cases diagnosed[29]. In settings considered to be of low-risk for esophageal cancer, the most frequent histological type varies between countries. Although EAC used to account for less than 15% of esophageal cancer cases, and this is still the situation for most populations, EAC has recently become the most common subtype in some Western countries, after an increase greater than the observed for any other cancer[30]. In the USA, EAC incidence increased by seven-fold between 1975 and 2006, and it now represents over 60% of all esophageal cancer cases[31]. In Europe, the UK and Nordic countries have also observed a steep increase in EAC incidence and it has become the predominant subtype in those settings, unlike Southern Europe, where ESCC remained the most common subtype until 1998[27].

Most esophageal cancer patients are diagnosed at an advanced stage of the disease, and although improvements have been described in some settings, five-year relative survival rates are usually below 20%[32]. In the USA, using information from 18 SEER geographic areas, the five-year relative survival in 2002-2008 was 16.9%, with higher rates being observed among white than black individuals, for both sexes[4]; however, a trend analysis by stage at diagnosis showed that survival increased from 33.5% to 47.8% for localized, from 9.4% to 20.7% for regional and from 1.9% to 2.9% for distant staged tumors, between 1992-1995 and 2000-2007[33]. In Europe, the EUROCARE-5 Project reported a five-year relative survival of 12.4% in 1999-2007, with an increase being reported between 1999-2001 and 2005-2007, from 9.9% to 12.6%[5]. Central Europe presented the highest survival in 1999-2007, while Eastern Europe had the lowest. These regions also had the biggest and smallest differences in five-year relative survival between the periods 1999-2001 and 2005-2007, of 4.3% and 0.8%, respectively[5].

Since esophageal cancer is a disease of poor prognosis, the measures of burden that evaluate disability show similar geographic and time patterns to the ones observed for mortality. Thus, the highest rates of disability-adjusted life years (DALYs) - computed based on the number of years of life lost (YLL) due to premature mortality in the population and the number of years lost due to disability (YLD) for people living with the disease or its consequences - are also observed in regions of high incidence[3]. Moreover, the Institute for Health Metrics and Evaluation estimated that the YLL component accounted for 98.7% of the DALYs worldwide, and that China alone contributed for 42.6% of the total DALYs related to esophageal cancer[34].

RISK FACTORS

Esophageal cancer risk is highly dependent on the age, sex and race of individuals. It is rarely diagnosed in children and young adults, becoming more frequent in the age groups above 45 years; rates increase exponentially with age until approximately age 60, showing a more modest increase thereafter[25]. As it was previously described, this cancer occurs more frequently among men than women, with male/female ratios often surpassing three-fold and reaching values of 8:1 for EAC, among white people[9]. The reasons for the gender disparity in EAC are not fully understood, but a greater proportion of abdominal fat or some unidentified influences of estrogen or testosterone on cancer development have been pointed out as possible explanations[35, 36]. Esophageal cancer also shows notorious racial and ethnic differences in incidence and mortality, which vary according to cancer subtype. In the USA, rates of EAC are higher among white than black men by more than three-fold, with white males also presenting a steeper increase in EAC incidence than black males[25], whereas for ESCC the rates among black men are over five-fold the ones observed among the white [37].

Regarding modifiable risk factors, several studies have assessed their effects on esophageal cancer incidence and mortality[6]. The contributions of each exposure to the occurrence of a specific outcome may be quantified using population attributable fractions (PAFs) which, by definition, constitute the proportional reduction in population disease or mortality that would occur if the exposure to a risk factor were reduced to a counterfactual scenario (e.g., no tobacco use).

Table 1. Individual and joint contributions of risk factors to mortality and burden of disease from esophageal cancer (source: Ezzati[38]).

Outcome	Risk factor	World	Low- and middle-income	High-income
Mortality	Alcohol use	26%	24%	41%
	Smoking	42%	37%	71%
	Low F&V intake	18%	19%	12%
	Joint PAF	62%	58%	85%
DALYs	Alcohol use	27%	25%	43%
	Smoking	42%	39%	71%
	Low F&V intake	19%	20%	13%
	Joint PAF	63%	60%	86%

F&V: fruit and vegetable; PAF: population attributable fraction; DALYs: disability-adjusted life years.

Table 1 depicts the individual and joint PAFs for three of the most commonly mentioned risk factors for esophageal cancer, namely alcohol drinking, tobacco consumption, and low fruit and vegetable (F&V) intake, as provided by the Global Burden of Disease Project for the year 2001[38]. The outcomes represent the percentage of burden measured as DALYs and deaths from cancer. Since separate risk factors can interact in their effect on the overall risk of disease, the sum of

individual PAFs may exceed 100%. When considering each risk factor individually, the highest PAFs were observed for smoking, and the lowest for insufficient F&V intake. Once again, the burden of disease measured as the number of DALYs yielded similar results to that of mortality from esophageal cancer, because of the high lethality of the disease. According to these estimates, in high-income countries, if smoking were reduced to the theoretical minimum risk exposure (defined as a prevalence of 0%), the burden of esophageal cancer would be 71% lower, while in the low- and middle-income region that proportion would be 39%. For alcohol drinking, the corresponding values would be 43% and 25%, respectively. For F&V intake, which had 600 grams/day as the theoretical minimum risk exposure, PAFs were higher for the low- and middle-income region, which means that a higher proportion of esophageal cancer cases in that region could be prevented through an adequate consumption of F&V than in the high-income region.

Although worldwide statistics of the burden of esophageal cancer attributable to modifiable risk factors are mainly, if not only, provided for esophageal cancer as a whole, the diverse etiologies of ESCC and EAC subtypes should be taken into consideration for a proper evaluation of the burden of disease in different settings.

The main risk factors for ESCC occurrence are tobacco smoking and alcohol consumption[4, 39]. A collaborative, population-based study undertaken in 1997 has reported that the risk of developing ESCC is more than five times higher among current smokers and almost three times higher among ex-smokers, when compared to never smokers[40]. A more recent study showed that both the duration and intensity of smoking are independently associated with ESCC, and that the cancer risk among ex-smokers remains higher for up to 30 years after cessation, even though the magnitude of the risk reduction was approximately 15-20% for every 10 years post smoking cessation[41]. Regarding alcohol consumption, the International Agency for Research on Cancer (IARC) Monograph published in 2010 provided consistent epidemiologic evidence that it is causally related to ESCC, while there is little or no association with EAC[42]. For ESCC, several studies have shown a dose-response relationship[32, 43]. A meta-analysis conducted in 2011, including 40 retrospective case-control and 13 prospective studies, estimated the relative risk for the association between ESCC and light, moderate and heavy alcohol drinking as 1.31, 2.27 and 4.89, respectively, although a significant publication bias was suggested by the results regarding heavy alcohol intake towards an overestimation of the results in this group[44]. The biologic effects of alcohol intake on the risk of digestive tract cancers depend on the individual's genotype. Individuals with the ALDH2 (aldehyde dehydrogenase 2) Lys487 allele have a deficiency of ALDH2, leading to a higher risk of esophageal cancer than that observed in individuals with no deficiency and consuming the same amount of alcohol[6]. Regarding tobacco smoking, studies have shown a strong association between tobacco-specific N'-nitrosonornicotine (NNN) and esophageal cancer risk, suggesting it as a causative agent for esophageal cancer among tobacco users[45]. In addition to the independent effects of smoking and alcohol drinking on ESCC, studies have also shown a synergistic effect of these determinants[46]. In the USA and other Western countries, more than 90% of ESCC cases have

been attributed to smoking and alcohol consumption[16, 39]. However, these factors seem to be less important for the burden of cancer in some high-risk areas of China and Iran[47, 48]. In these regions, the prevalence of exposure to smoking and alcohol is low[49], and other suggested risk factors include poor nutrition, the consumption of beverages at high temperatures and the use of opium[39, 48, 50, 51].

The consumption of fruits and vegetables has been described as a protective factor for the occurrence of ESCC[52]. This has led to trials evaluating the inhibitory effect of supplements or micronutrients on tumor growth, in areas with high incidence rates. One of the largest studies was conducted in Linxian, China, involving approximately 30 000 individuals, randomized to receive specific combinations of vitamins and minerals[53]. After five years of supplementation, mortality rates decreased by 13% among those receiving a combination of beta-carotene, vitamin E and selenium. Another trial in the same area, on 3 000 individuals with dysplasia, found a decrease in mortality from a supplementation using several vitamins and minerals[54]. Although other studies have found no reduction in the prevalence of esophagitis[55, 56], evidence suggests that improvements in nutrition may contribute to lower esophageal cancer incidence.

Most studies on the association between socioeconomic status and esophageal cancer have been conducted in high-risk populations, and evidence shows that socioeconomic status is inversely associated with ESCC, while inconsistent results have been found for EAC[16, 57, 58].

A strong association between GERD symptoms and EAC has been described, with estimated odds ratios (OR) ranging from 5 to more than 40[15, 31, 59], a variability that reflects the increase in risk with the duration, frequency and severity of symptoms. Given the markedly increased risk of EAC among GERD patients, and the influence that GERD also has on the development of BE, some authors have suggested chemopreventive measures to hinder the transition from normal squamous epithelium to EAC. Although conflicting results have been found between some observational studies[60, 61], an inverse association between the use of nonsteroidal anti-inflammatory drug (NSAID) and the risk of EAC has been found in several systematic reviews[62, 63]. H_2 receptor antagonists (H_2 blockers), such as cimetidine and ranitidine, reduce acid production in the stomach, which may reduce the risk of EAC by decreasing the acid content in GERD. However, they may also increase risk by neutralizing the gastric pH, leading to the proliferation of bacteria in the stomach and an increasing production of carcinogens including nitrosamines and acetaldehyde. Several studies have evaluated the effect of H_2 blockers on EAC risk, but results were inconclusive, with authors suggesting confounding by reflux[64-66]. More recently, studies focusing on proton pump inhibitors have suggested a decreasing risk of EAC with their use, although evidence on this association is still limited[60, 67]. Inconsistent results were also found regarding medications that relax the lower esophageal sphincter, such as calcium channel blockers and benzodiazepines, which might increase EAC risk[16].

Regarding obesity, a strong and dose dependent association with EAC has been observed, independent of GERD[14]. The systemic inflammatory state led by the altered metabolism of

obese patients, and the associated impact of adipocytokines and pro-coagulant factors released by adipocytes in central fat, has been proposed as an explanation for the association between obesity and EAC[68]. Parallel trends of the prevalence of overweight and obesity to those observed for EAC incidence further support the idea that obesity is a central driver of BE and EAC rates[68].

The association between smoking and EAC is much weaker than that of ESCC[69]. A meta-analysis conducted in 2011 on the relation between EAC and tobacco smoking yielded relative risks of 1.8, 2.3 and 1.6, respectively for ever, current and ex-smokers, in comparison with never smokers[70]. Furthermore, the authors have found a direct association with dose and duration of cigarette consumption. A population-based case-control study assessed the effect of smoking cessation in EAC risk and showed that the risks among ex-smokers remained considerably high until 20 years after cessation, although no evidence was found that smoking intensity influenced the risk of EAC[41].

Reviews published in 2003 and 2007, respectively by IARC and by the World Cancer Research Fund and the American Institute for Cancer Research, found an inverse association between F&V intake and esophageal cancer risk, especially when considering case-control studies[71, 72]. Few prospective studies have investigated the effect of F&V intake on EAC and ESCC separately, and the association seemed weaker for EAC[73, 74]. On the other hand, consumption of meat and high-fat meals has been found to be positively associated with EAC[72, 75].

H. pylori infection is also inversely associated with the occurrence of EAC, regardless of other environmental and genetic exposures[76], and the decline in the prevalence of this infection may have contributed to an increase in EAC incidence. The mechanism through which *H. pylori* infection reduces the risk of EAC is not clear, but studies have suggested that the bacteria could decrease gastric acid secretion by acting on parietal cells or through chronic inflammation[77].

Since tumors arising in the cardioesophageal junction are classified as cardia cancers, according to the International Classification of Diseases for Oncology[78-80], the increasing awareness of EAC may also have led to the increase in its incidence trends, through a misclassification of gastric cardia cancers[81]. However, in some settings, the incidence of cardia cancer is also increasing, and countries with the highest cardia rates present the highest EAC rates, so this misclassification should be further assessed for the clarification of observed trends[14, 81, 82].

The evidence summarized here suggests that there is room for lowering the worldwide burden of disease related to esophageal cancer through the implementation of public health strategies to reduce risk in specific populations. Once the most important modifiable risk factors are defined, the evaluation of potential interventions should take into account their joint effect on the current and future burden of disease in each setting.

METHODS FOR PREDICTION OF THE BURDEN OF CANCER

Predictions of cancer incidence and mortality can be used to better inform decision-making policies, and aid in the efficient allocation of resources to meet short-term needs for cancer prevention, detection and treatment. However, since past trends will not necessarily persist in the future, a certain level of uncertainty is present in all projected values[83].

Several statistical methods have been used to predict the future burden of cancer. The simplest methods are usually applied in order to obtain short-term predictions (e.g., up to five years past diagnosis), by assuming the persistence of past rates or trends into the future. However, predictions over a longer term require more complex models, which aim to quantify the contribution of specific variables to the observed changes in the past, while making assumptions about the extent to which past changes are likely to influence the future. This increasing complexity in the models used for cancer prediction depends on the level of detail in data available for analyses (Figure 4).

In this section, the rational for different types of prediction models is presented, discussing their advantages and shortcomings.

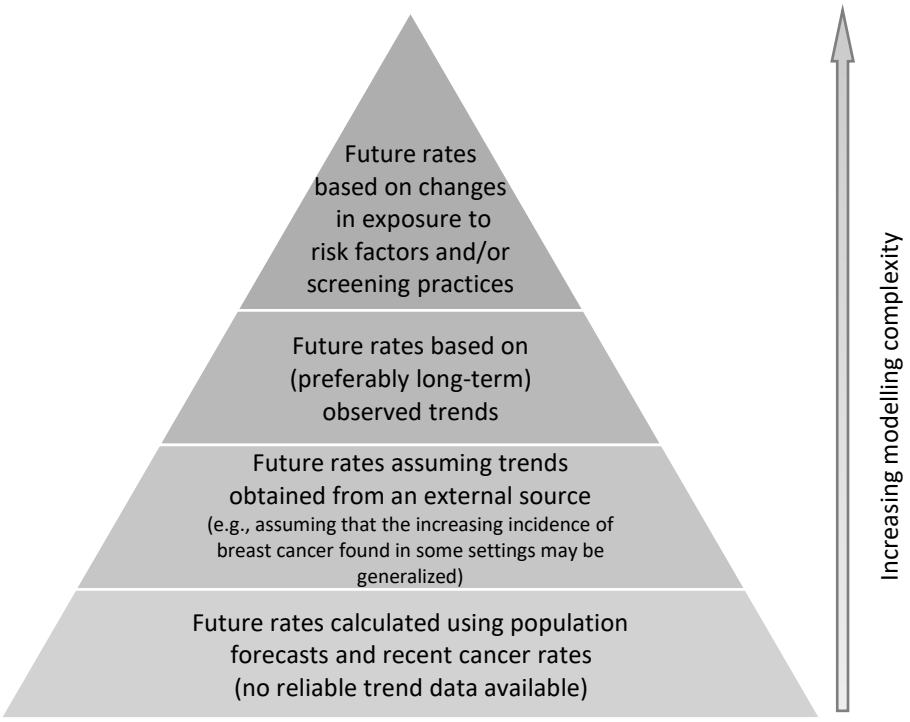

Figure 4: Increasing complexity of prediction models depending on data availability (adapted from Bray[83]).

APPLICATION OF CURRENT INCIDENCE RATES TO FUTURE POPULATION ESTIMATES

The simplest method to perform predictions, which is used by the GLOBOCAN Project[84], is the direct application of current incidence or mortality rates to the future expected population in the year of interest. Age is the most important time-related variable that influences cancer risk[83]. In GLOCOBAN 2012, the expected number of new cancer cases or deaths in a country/region in 2015-2035 was computed by multiplying the age-specific incidence and mortality rates estimated for 2012, by the expected population for 2015-2035. This expected population differs from that of the baseline year in terms of age structure and size.

Although the assumption that past rates will remain in future years may hold true in short-term predictions and for specific cancer sites, it is arguable that this will remain accurate in the longer-term ones. This method does not accommodate for changes in trends over time, leading to an underestimation of future incidence or mortality rates in cases of upward trends, and an overestimation in the opposite situation. However, since no reliable information regarding past trends is available for analysis in several regions in the world[85], it poses as the only solution for performing cancer incidence predictions worldwide.

AGE-PERIOD-COHORT AND AGE-PERIOD MODELS

Period effects relate to events that change incidence and mortality in a similar manner across all age groups. Examples of such events include changes in classification criteria, for incidence, or advances in treatment, for mortality. Cohort effects cause changes in incidence and mortality rates from one generation to another that are consistent across age groups. Many lifestyle factors, such as tobacco smoking, sexual and reproductive behaviors, are influenced by the date of birth, and cohort effects have an important role in the confirmation/refutation of putative etiological factors from other studies[83]. The application of an age-period-cohort (APC) model to perform predictions usually involves estimating the underlying age-, period- and cohort-specific trends and projecting them into the future using a Poisson regression model. Since the three components are codependent (e.g., for a given date of birth and age, the time period is locked), such models allow for the estimation of the average increase/decrease over time, but do not allow to disentangle the variations due to period effects from those of cohort effects. This average underlying trend, common to both period and cohort components, is named the "drift"[86].

From tabulated data using five-year age groups and five-year calendar periods, birth cohorts are obtained by subtracting age from period. The APC model can be written as:

$R_{ap} = \exp(A_a + D.p + P_p + C_c)$, where R_{ap} is the incidence rate in age group a and calendar period p; A_a is the age component for age group a; D is the drift; P_p is the non-linear period component of period p; and C_c is the non-linear cohort component of cohort c.

A problem with this function of the APC model is that it yields exponentially growing predictions which are unrealistic for some cancer types. A proposed solution for this limitation, developed in Nordic European countries, was a power model which reduces the predicted rates growth by replacing the exponential x by the functional form x^5. This method, called Nordpred, was found to improve predictions by a comparative study of different approaches[87], and has been widely used since[88, 89].

The Nordpred method has been used by the World Health Organization (WHO) Mortality Database to perform long-term predictions[90]. For each combination of country, cancer, sex and the latest year of observation, the model requires at least 15 consecutive years of data (in order to build three five-year periods), with a minimum of 100 deaths recorded per five-year period to allow for stability in the results, and predicts up to five five-year periods (25 years ahead). The results are presented by age group and for all ages combined. For each predicted period, the online tool then divides the number of predicted deaths in two parts: one due to changes in risk of dying from cancer, and another due to changes in the population size and structure[90].

For cancers with a small number of cases, a Bayesian approach has also been proposed for the application of an APC model[91]. With this methodology, the parameters of the usual APC model are assessed through their credibility intervals, instead of being considered as fixed values.

When long-term data are not available for analysis, it is difficult to evaluate cohort patterns through an APC model[83]. For these situations, there are simpler models which have been derived by Dyba and Hakulinen, the so-called DH models, using only the age and period components[92, 93]. The underlying assumptions of the proposed models are as follows: future cancer trends can be modelled by extrapolating a historic trend; there are enough years of data available to allow for the estimation of models which incorporate age- and sex-specific trends; the numbers of cases/deaths in each age, sex and time period stratum follow a Poisson distribution. Additionally, when historic trends (of age-standardized rates) are decreasing, a log-linear model is suitable to estimate the average rate; otherwise, a linear model is used to avoid exponential growth. Although these models do not include the cohort component, they have also shown a good performance when compared to other methods[87] and are used by the WHO Mortality Database to perform short-term predictions (up to five years past the year of death)[90].

Another example of an age-period model is the Joinpoint software, even though it has been mainly applied to detect significant changes in cancer trend analyses[94]. In this method, cancer incidence and mortality rates are modeled based on the least squares method as a function of time, which is composed of piecewise linear segments, connected at the so-called "joinpoints". The program starts by adjusting a straight line (e.g., 0 joinpoints) to the trend data and progressively tests the statistically significance of adding more joinpoints to the model, up to the maximum number defined by the user. The tests of significance use a Monte Carlo Permutation method[95]. The models may incorporate estimated variation for each point or use

a Poisson model of variation. Fitted models may be linear or log-linear, the latter being useful to calculate annual percentage rate changes. The software then provides the point and interval estimates of the slope parameters, allowing for the extrapolation of observed trends into the future.

THE STATE-SPACE MODEL

The State-Space model (SSM) has been used in the USA by the National Cancer Institute/American Cancer Society to predict cancer mortality three years ahead of the current calendar year since 2004[96]. It consists of two main steps: a measurement equation and the transition equation[97]. First, the model assumes that the number of deaths follows a linear model with time-varying coefficients, which also follow a linear model. This yields a quadratic trend over short segments of time. Second, a transition equation is used to model the year-to-year variation of the parameters (or states). Random errors are incorporated in both equations, with error variances being estimated from the data[98]. The measurement and the transition equations are combined to obtain the full specification of the SSM. The model is then projected three years into the future, yielding the number of deaths and corresponding 95% prediction intervals.

Due to the time-varying coefficients considered by the SSM, it can adjust to unexpected changes observed in the data, being more flexible than a standard regression model. However, the sensitivity of the SSM to these changes can be a limitation when they are due to random variations. To overcome this problem, two additional parameters – which are estimated by minimizing the sum of squares of the differences between the observed number of deaths and their three-year-ahead predictions – are included in the model, to refine the calculation of error variances[96].

MICRO-SIMULATION MODELS

Mathematical models are powerful tools which can be used to perform predictions by systematically aggregating available data. However, a major criticism to this methodology is that independent modeling efforts frequently produce contrasting results. Generally, these differences are due to diverse model inputs and configurations, as well as to the lack of transparency in model assumptions. In the USA, the Cancer Intervention and Surveillance Modeling Network (CISNET), a National Cancer Institute funded consortium, aims to overcome these limitations by using a comparative modeling approach. The CISNET consortium focuses on five cancer sites: breast, colorectal, lung, prostate, and esophagus. Moreover, CISNET models have been used by the United States Preventive Services Task Force for breast and colorectal cancer screening guidelines[99, 100].

Since 2011, three esophageal cancer modeling groups have been collaborating as part of CISNET, all focusing on EAC: the MSEAC model, from the Fred Hutchinson Cancer Research Center; the EACMo model, from the Massachusetts General Hospital; and the MISCAN-ESO model, from the University of Washington and Erasmus University Medical Center[101]. MSEAC is a biological model assuming that the accumulation of mutations and clonal expansion of altered cells forms the basis for carcinogenesis, and it is built on likelihood and micro-simulation methods[102]. EACMo is a Markov state transition simulation model, which simulates a cohort of individuals and does not allow for disease regression[103]. MISCAN-ESO is also a micro-simulation model, which allows for disease regression in the health states prior to cancer. The three models include the following health states: healthy, GERD, BE with and without dysplasia, preclinical cancer, clinically diagnosed cancer and death. The EACMo and the MISCAN-ESO models also classify dysplasia in BE as low- and high-grade.

All models are calibrated to EAC incidence and mortality data collected from SEER, for all men and women aged 20-84 years, from 1975-2010. Moreover, the three groups use a generalization of APC[86, 104] to model EAC increase, in which age, period, and cohort trends are applied to rates within the natural history model. These models have recently been used to perform EAC incidence and mortality predictions for the year 2030[101]. Although the three groups differ in their modeling structure, they all yield predictions as a function of age and stage.

THE PREVENT MODEL

PREVENT was originally developed in 1988 and is defined as a multiple risk factor, multiple disease dynamic population model that allows the user to evaluate the effects of risk factor interventions. From observed changes in the exposure to a risk factor and the relative risk between that factor and the disease of interest, PREVENT estimates the proportional change in disease risk that would occur if the exposure reached a theoretical minimum value (e.g., smoking prevalence of 0)[105]. After the user specifies a change in risk factor prevalence due to an intervention, PREVENT calculates future incidence rates using observed and predicted changes in disease risk, and attributes the difference between the two to the intervention. Although some authors have performed cancer predictions using this method[106, 107], results are not easily reproducible since the software is not freely available and there is no full explicit formulation of the methods involved. Furthermore, such an approach requires a continuous update of the information regarding the relation between different modifiable risk factors and the different cancers, or their subtypes with distinct etiologies, to reflect the state of the art of the understanding of causes of different cancers.

A conceptually similar approach underlies the IMPACT model, which was originally developed in the 1990s by Capewell and colleagues to explain the declining mortality from coronary heart disease, and to develop a comprehensive model of policy and prevention of the disease[108].

After its first application to data from Scotland, it has henceforth been validated in 2001, gradually refined and widely used in more than 20 populations[109-111].

The main objective of the authors was to build a conceptually simple, although methodologically sophisticated model, with explicit assumptions that undergo multiway sensitivity analyses. The method takes into consideration the following components:

- Major risk factors, including smoking, cholesterol, age and gender;
- Patient groups, such as subjects with angina and heart failure;
- Treatments, namely medication and surgery, and the cost-effectiveness of treatment;
- Outcomes, measuring death, survival rates and life-years gained in adults.

The model combines data from many sources on patient numbers, treatment uptake, treatment effectiveness and risk factor trends, measuring the consequent mortality effects, expressed as the number of deaths prevented or postponed (DPPs)[108].

Two approaches are used to calculate DPPs. A regression approach is used for continuous variables, for which DPPs are calculated as the product of three variables: the number of cases expected in the end year, the absolute reduction in the mean exposure between the two periods of interest and a regression coefficient quantifying the increase in risk of developing the disease by a unit increase in the mean exposure. Natural logarithms are used, assuming a log-linear relationship between changes in risk factor levels and mortality.

For categorical variables, a PAF approach is used. The PAF is calculated conventionally as $(P \times (RR - 1))/(1 + P(RR - 1))$, where *P* is the prevalence of the risk factor and *RR* is the relative risk associated with that risk factor.

The number of DPPs is then estimated as the number of deaths expected in the end year (had rates in the first year persisted), multiplied by the difference between the PAF in both periods. The numbers of DPPs as a result of risk factor changes are quantified systematically for each age and sex group to account for potential differences in effect. Due to the uncertainty surrounding these estimates, sensitivity analyses are then performed using the analysis of extremes method[112], generating minimum and maximum estimates for DPPs.

This method quantifies the contribution of each component to the observed variation in mortality, allowing for the assessment of potentially relevant interventions at a population level, in a similar way to that presented for the PREVENT model. Although the IMPACT model was not originally developed for cancer, the detailed description of the methods involved allow for their application in another context, had the proper and necessary adjustments been made to accommodate the disease under analysis.

DATA SOURCES FOR CANCER PREDICTIONS

Cancer predictions rely, first and foremost, on the high quality of incidence and mortality data, and of population forecasts. While data on population forecasts are easily obtainable from international (such as the United Nations[113]) or local (national statistics offices in each country) sources of information, cancer incidence and mortality data require more careful attention.

Reliable monitoring and surveillance of cancer is crucial for cancer control policies. Cancer registries are expected to accomplish this demand by collecting cancer incidence data for defined populations, including information on patient and tumor characteristics at diagnosis and, in some instances, stage at diagnosis, treatments provided and patient´s follow-up.

However, the quality of incidence data provided by population-based cancer registries differs widely by geographic region, with many countries in Latin America, Asia and Africa presenting a poor quality or even total absence of information (Figure 5). Aiming at the development of cancer registration in such areas within the next decade, IARC has brought together diverse partners and created the Global Initiative for Cancer Registry Development[85]. This project has developed six Regional Hubs aimed at providing localized training and support for the development of cancer control plans and research networks.

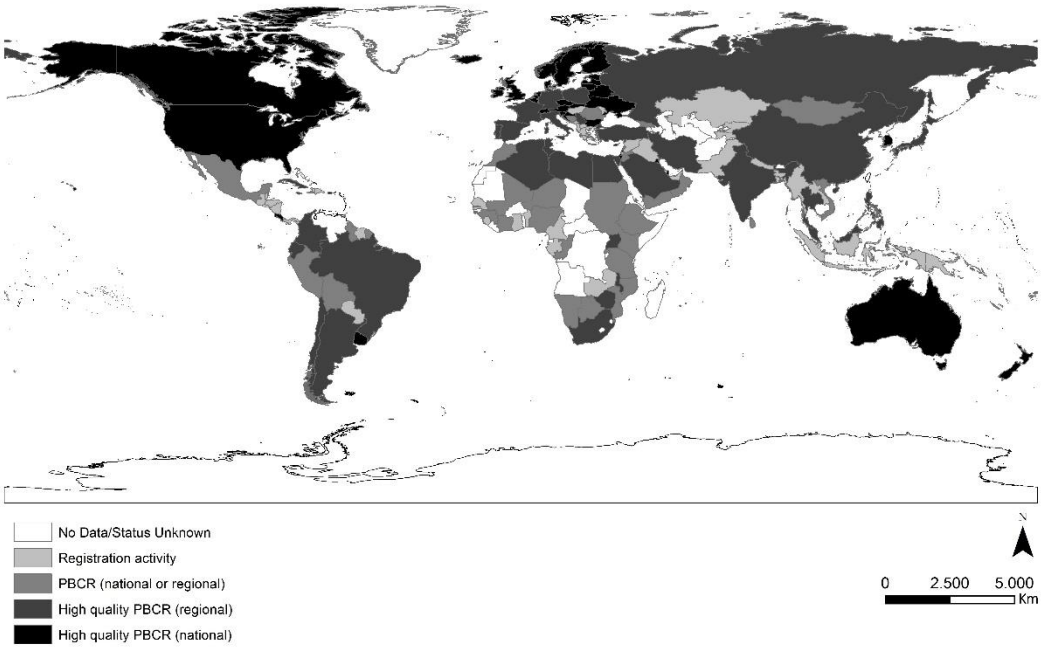

Figure 5. Quality of regional/national population-based cancer registries (source: Bray[85]).

The International Association of Cancer Registries (IACR), founded in 1966, represents population-based cancer registries worldwide. Every five years, IACR works in collaboration with IARC to gather incidence data from high-quality registries and to present data in a publication entitled Cancer Incidence in Five Continents (CI5). Information published in CI5 is then used for worldwide cancer incidence estimates provided by the GLOBOCAN Project[84]. For countries/regions where no cancer registry data are available, incidence is estimated from mortality information and/or from incidence data in adjacent areas.

The number of registries with available data in CI5 has increased over time, from 32 (in 29 countries) in Volume I to 290 (in 68 countries) in Volume X[114]. These publications present the absolute numbers of cancer cases by period, age group, sex, cancer site and the corresponding populations at risk. In addition, there is also an online database, CI5plus, containing updated annual incidence rates for 118 selected populations from 102 of the cancer registries included in CI5, for the longest period available up to 2007, for all cancers and 27 major types[115]. CI5plus can be used for time trends analyses, but these should be interpreted with caution because of differences in registration practices and coding over time, as well as the existence of missing data for specified cancer subsites or histological types[115].

In Europe, the first cancer registry was established in Hamburg, Germany, in 1927. In the 1940s and 1950s, regional registries were also developed in the UK and other countries. In Denmark, a national cancer registry was created in 1942. In Portugal, three regional cancer registries were established in 1988 on a legal framework (government decree 35/88 of January 16th), yielding a 100% coverage of the national mainland territory. The North Region Cancer Registry (RORENO) covers a population of approximately 3.2 million people (nearly 30% of the Portuguese population) and is located in the Portuguese Oncology Institute of Porto. It constitutes the main source of information on cancer burden in Northern Portugal, publishing annual reports on cancer incidence and mortality/incidence ratios in the region. Incidence data from RORENO have been included in CI5 Volume IX[116], while survival data have been published in local and international studies such as EUROCARE-5[117] and CONCORD-2[118]. Apart from the initial years of operation, in which the completeness of registration is expected to be lower, the functioning and resources involved in cancer registration in the region have been fairly stable, and a quantitative study on the completeness of the registry yielded favorable quality results[119].

Regarding mortality, there is also great variation in the availability of information, as well as in the quality of data obtainable, with several countries of low and medium Human Development Index presenting low levels of quality and completeness of death certificate information (Table 2). Although in some settings, as in the USA, registries have access to cancer mortality data from death certification, this is not the case for a large number of registries. However, there is an online tool (WHO Mortality Database) which compiles mortality data as reported annually by WHO Member States from their civil registration systems[90]. The WHO Mortality Database

provides access to the number of deaths and age-standardized mortality rates by country, year, cause of death and sex. Causes of death are coded according to the 9th and 10th editions of the International Classification of Disease (ICD-9, ICD-10), since 1979. More detailed information is available in raw data files for download, together with the necessary instructions, file structures and code reference tables, from 1950 onwards.

Table 2. Proportion (%) of regional coverage by high quality cancer registration and high quality complete vital registration of death (source: Bray[85]).

	High quality cancer registration data	High quality complete vital registration of death
Africa	2%	0%
Asia	6%	3%
Northern America	95%	100%
Latin America and the Caribbean	8%	25%
Oceania	78%	74%
Europe	42%	18%

In order to collect data on the prevalence of exposure to risk factors, one of the major sources of available information is the WHO Global InfoBase[120]. This online repository provides country-level data on relevant risk factors for non-communicable diseases, for all WHO Member States. It gathers information collected from different surveys conducted in each country, covering eight major risk factors: tobacco use, alcohol consumption, F&V intake, overweight and obesity, raised blood pressure, raised cholesterol, physical inactivity and diabetes. All available information may be traced back to its original source. The WHO Global InfoBase collaborates with WHO Regional Offices to ensure the most up to date information possible.

Furthermore, WHO provides worldwide relevant information on risk factors in dedicated databases and reports, which are freely available from the Global Health Observatory Data Repository[121]. The Global Information System on Alcohol and Health (GISAH)[122] provides information on levels (*per capita* availability) and patterns of alcohol consumption (prevalence of consumers and abstainers), by country and by year, as well as information on economic aspects, existing control policies and other key indicators for non-communicable diseases. The WHO Tobacco Free Initiative is composed by three units: National Capacity Building, Comprehensive Information Systems for Tobacco Control and Tobacco Control Economics. It aims to surveil the global tobacco epidemic and to assist countries in enhancing their ability to resist the epidemic of tobacco through the implementation of the WHO Framework Convention on Tobacco Control. The progress of WHO Member States towards the execution of suggested measures is routinely reported through the WHO Report on the Global Tobacco Epidemic[123]. Regarding overweight and obesity, information provided at the Global Health Observatory Data Repository concerns the prevalence of overweight and obesity and mean body mass index (BMI) by country, year and sex. For more detail, there is also information at the WHO Global Database

on BMI[124], which allows the user to obtain national and sub-national BMI data. Alcohol and tobacco consumption, and overweight and obesity are here presented as examples, but information on other risk factors is also attainable from WHO dedicated websites.

Despite the existence of several worldwide sources of information for some of the most commonly evaluated risk factors, more detailed data regarding the same or other determinants (e.g., stratified results by age and sex) may be found in national/local sources, such as national health surveys or national statistics offices, as well as in scientific or technical publications of survey data, which should not be disregarded when looking for the most accurate information possible.

AIMS

Despite the extensive knowledge on the main risk factors for esophageal cancer, their joint contribution for the trends in the burden of disease associated with esophageal cancer has not been formally assessed.

This research aimed to translate the accumulated knowledge on the etiology of esophageal cancer into a model able to describe and predict the variation in its incidence at a population level, taking into account the variation in the exposure to the main modifiable risk factors.

The development of such a model required the accomplishment of the following specific objectives:

1. To describe the trends in esophageal cancer incidence, overall and by histological type, in different countries, including Portugal (Papers I-III);
2. To summarize the evidence on the exposure to the different risk factors of esophageal cancer in Northern Portugal over the past decades (Paper III);
3. To summarize the current scientific knowledge on modifiable risk factors for esophageal cancer, by histological type, through a systematic review of published meta-analyses (Paper IV);
4. To estimate the contribution of the variation in the exposure to the main risk factors for esophageal cancer to changes in its incidence rates between 1995 and 2005, in Northern Portugal and in selected countries (Paper V).

The accomplishment of these objectives was based on the collection of data from numerous sources of information. Cancer incidence data were retrieved from RORENO and from CI5 publications. The levels of exposure to risk factors were derived from online databases provided by WHO, national health and nutrition surveys and literature searches. The strength of association between each risk factor and esophageal cancer was obtained from a systematic review of meta-analyses. The methods are described in detail in each of the papers that constitute this thesis.

PAPERS

Paper I

Castro C, Bosetti C, Malvezzi M, Bertuccio P, Levi F, Negri E, La Vecchia C, Lunet N.

PATTERNS AND TRENDS IN ESOPHAGEAL CANCER MORTALITY AND INCIDENCE IN EUROPE (1980-2011) AND PREDICTIONS TO 2015.

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Patterns and trends in esophageal cancer mortality and incidence in Europe (1980–2011) and predictions to 2015

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Background: Over the last few decades, esophageal cancer incidence and mortality trends varied substantially across Europe, with important differences between sexes and the two main histological subtypes, squamous cell carcinoma (ESCC) and adenocarcinoma (EAC).

Patients and methods: To monitor recent esophageal cancer mortality trends and to compute short-term predictions in the European Union (EU) and selected European countries, we analyzed data provided by the World Health Organization (WHO) for 1980–2011. We also analyzed incidence trends and relative weights of ESCC and EAC across Europe using data from Cancer Incidence in Five Continents.

Results: Long-term decreasing trends were observed for male esophageal cancer mortality in several southern and western European countries, whereas in central Europe mortality increased until the mid-1990s and started to stabilize or decline over the last years. In some eastern and northern countries, the rates were still increasing. Mortality among European women remained comparatively low and showed stable or decreasing trends in most countries. Between 2000–2004 and 2005–2009, esophageal cancer mortality declined by 7% (from 5.34 to 4.99/100 000) in EU men, and by 3% (from 1.12 to 1.09/100 000) in EU women. Predictions to 2015 show persistent declines in mortality rates for men in the EU overall, and stable rates for EU women, with rates for 2015 of 4.5/100 000 men (about 22 300 deaths) and 1.1/100 000 women (about 7400 deaths). In northern Europe, EAC is now the predominant histological type among men, while for European women ESCC is more common and corresponding rates are still increasing in several countries.

Conclusion(s): The observed trends reflect the variations in alcohol drinking, tobacco smoking and overweight across European countries.

Key words: esophageal neoplasms, Europe, histologic type, incidence, mortality, trends

introduction

Esophageal cancer incidence and mortality trends varied substantially across Europe over the last few decades, with important differences between sexes and the two main histological subtypes, squamous cell carcinoma (ESCC) and adenocarcinoma (EAC) [1].

Among men, there were marked long-term declines in mortality in southern European countries such as France and Italy, whereas upward trends were observed up to the most recent years in the UK, the Netherlands and Romania [1]. In the European Union (EU) as a whole, male age-standardized mortality rates decreased between 1990–1994 and 2000–2004 from 5.7 to 5.4/100 000, while female rates remained stable around 1.1/100 000 [2].

ESCC was the main histological type in most European countries, though steady increases in EAC incidence were observed in several regions. In the late 1990s, EAC was already more frequent than ESCC in some northern European countries, such as Denmark and Scotland [1].

To monitor recent mortality trends and to compute short-term predictions of esophageal cancer mortality rates in the EU and selected European countries, we analyzed mortality data provided by the World Health Organization (WHO). We also analyzed the trends in incidence rates of ESCC and EAC and the relative weight of these main histological types of esophageal cancer across Europe.

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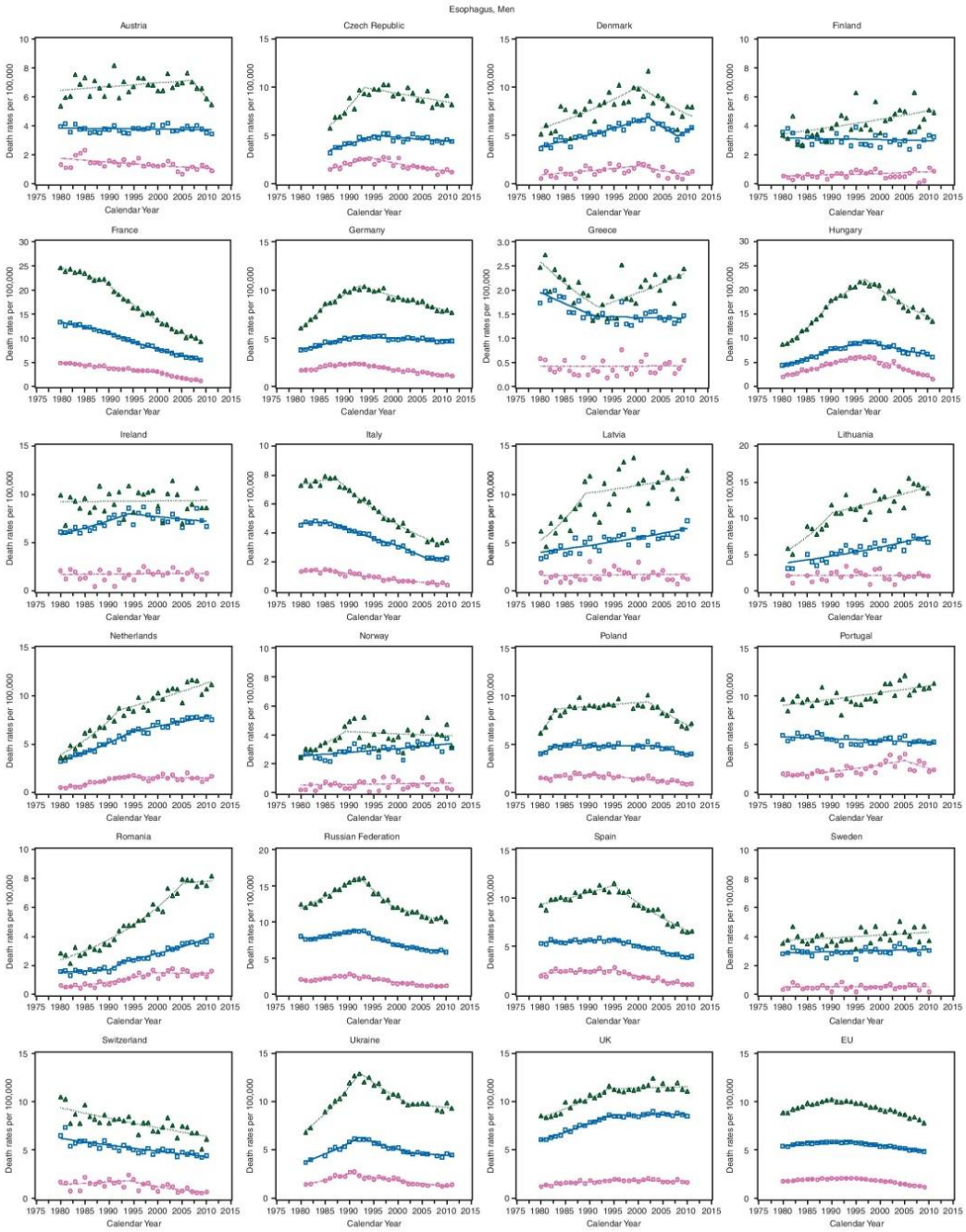

Figure 1. Joinpoint analysis for age-standardized (world population) mortality rates per 100 000 men for esophageal cancer (all ages and truncated at 25–49 and 35–64 years) in selected European countries, 1980–2011. □–□, all ages; ○– –○, 25–49 years; △–△, 35–64 years.

methods

Official data for esophageal cancer mortality in the EU and selected European countries over the period 1980–2011, and the corresponding population figures, were derived from the WHO database [3]. Since in the period considered three different Revisions of the International Classification of Diseases (ICDs) were used to classify esophageal cancer deaths, death certification numbers corresponding to codes A046 (ICD-8) [4], B090 (ICD-9) [5] and C15 (ICD-10) [6] were extracted, as applicable. Country- and sex-specific mortality rates were computed for each 5-year age group (0–4, …, 75–79, 80+) and calendar year, and age-standardized rates were calculated at all ages and truncated at 25–49 and 35–64 years (direct method, world population). Mortality rates for the EU as a whole were computed using the aggregated number of deaths, and corresponding populations, in its 27 Member States, as defined in January 2007; Cyprus was excluded due to limited data available.

Poisson regression analysis was carried out using the Joinpoint software [7] in order to identify significant changes in the mortality trends, allowing for up to three joinpoints.

For selected European countries and the EU as a whole, we provided predicted numbers of esophageal cancer deaths and rates for the year 2015. These were derived by fitting a joinpoint model to each 5-year age-specific (age groups 0–4, …, 75–79, 80+) number of certified deaths, assuming a Poisson distribution, to identify the most recent trend segment. Then, a linear regression was carried out on mortality data for each age group over the most recent trend provided by the joinpoint model, to compute the predicted age-specific number of deaths, the corresponding 95% confidence intervals (CIs) and prediction intervals (PIs) [8]. Population figures for 2015 were obtained from EUROSTAT [9].

Incidence data were obtained from the Cancer Incidence in Five Continents (CI5) databases [10, 11] and analyzed by histological type. For countries with more than one cancer registry, data were aggregated to ensure the highest geographic coverage and the analyses were restricted to the longest common calendar period between registries.

Annual data for the period 1980–2002 (the last available year) were derived from the CI5-plus database [10], and 3-year moving averages were used to represent the histology- and sex-specific incidence trends in age-standardized incidence rates (direct method, world standard population).

Grouped incidence data, referring mostly to the period 1998–2002, provided by CI5 volume IX (CI5-IX) [11] were also retrieved, and used to describe the geographical distribution of esophageal cancer histological types across Europe, using ArcGIS [12].

results

In the EU as a whole, male esophageal mortality rates decreased since the early 1990s (all ages: APC = −1.2% in 1994–2009) with steeper declines since the early 2000s in younger age groups. Decreases in overall male mortality trends were observed in France, Greece, Italy, Portugal and Switzerland. Over the most recent calendar years, trends have also been decreasing or leveling off in the Czech Republic, Germany, Hungary, Ireland, Poland, the Russian Federation, Spain,

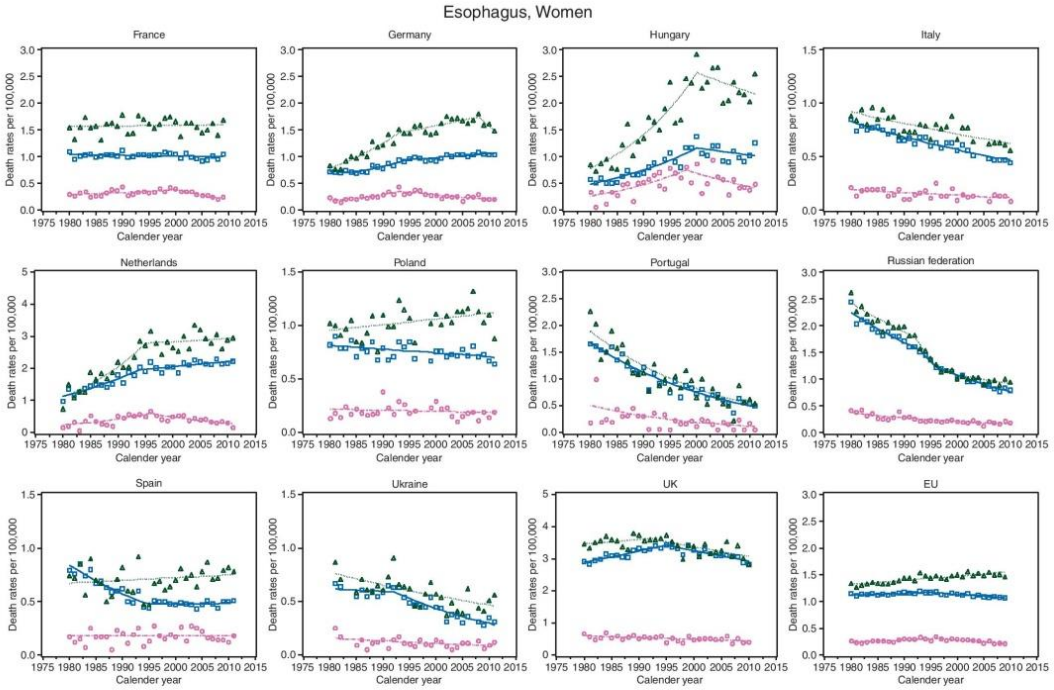

Figure 2. Joinpoint analysis for age-standardized (world population) mortality rates per 100 000 women for esophageal cancer (all ages and truncated at 25–49 and 35–64 years) in selected European countries, 1980–2011. □–□, all ages; ○–○, 25–49 years; △–△, 35–64 years.

Ukraine and the UK, whereas increasing trends were still observed in Latvia, Lithuania, the Netherlands, Norway and Romania (Figure 1 and supplementary Table S1, available at *Annals of Oncology* online).

Among EU women, esophageal cancer mortality started to decline in the mid-1990s at all ages (APC = −0.6 in 1995–2009) and in the age group 25–49 years (APC = −2.9 in 1996–2009), while for the 35–64 year age group a slight upward trend was observed over the period 1980–2009 (APC = 0.5%). Long-term decreasing trends were observed for overall female mortality in Italy, Poland, Portugal, the Russian Federation and Ukraine, and more recent declines (since the mid/late 1990s) were observed in Hungary and in the UK, whereas in Germany, the Netherlands and Spain increasing mortality trends were still observed over the most recent calendar years (Figure 2 and supplementary Table S1, available at *Annals of Oncology* online).

Between 2000–2004 and 2005–2009, in the EU as a whole, esophageal cancer mortality fell by 7% at all ages among men (from 5.34 to 4.99/100 000) and by 3% among women (from 1.12 to 1.09/100 000). The UK, particularly Scotland, had the highest overall mortality rate in 2005–2009 for both sexes, whereas Greece showed the lowest one among men (1.38/100 000) (Tables 1 and 2).

Table 1. Age-standardized (world population) mortality rates from esophageal cancer per 100 000 men (at all ages and truncated at 25–49 and 35–64 years) in selected European countries and in the European Union (EU) in the periods 2000–2004 and 2005–2009 (unless otherwise mentioned in parenthesis), and corresponding percent changes

	All ages			25–49 years			35–64 years		
	2000–2004	2005–2009	% change	2000–2004	2005–2009	% change	2000–2004	2005–2009	% change
Austria	3.81	3.88	2	1.24	1.03	−17	6.81	6.96	2
Belarus (2000–2003/2007–2009)	5.27	5.59	6	1.57	1.55	−1	10.57	11.15	5
Belgium (2003–2004)	5.47	5.20	−5	1.74	1.44	−17	9.01	8.64	−4
Bulgaria	1.99	2.43	22	0.79	0.98	24	3.89	4.78	23
Croatia	5.35	5.02	−6	1.84	1.39	−24	9.60	9.40	−2
Czech Republic	4.74	4.48	−5	1.90	1.38	−27	9.24	8.51	−8
Denmark	6.44	5.39	−16	1.63	0.93	−43	9.64	7.34	−24
Estonia	4.67	5.22	12	1.16	1.17	1	8.63	9.84	14
Finland	2.90	2.92	1	0.51	0.48	−6	4.46	4.67	5
France	7.19	5.99	−17	2.46	1.46	−41	12.58	10.24	−19
Germany	4.94	4.80	−3	1.57	1.30	−17	8.97	8.21	−8
Greece	1.49	1.38	−7	0.42	0.40	−5	2.08	2.09	0
Hungary	8.28	7.08	−14	4.55	3.00	−34	19.32	15.77	−18
Iceland	3.76	5.28	40	1.13	0.66	−42	4.52	6.72	49
Ireland	7.62	7.36	−3	1.96	1.57	−20	9.51	8.79	−8
Italy (2000–2003/2006–2009)	2.87	2.22	−23	0.66	0.52	−21	4.27	3.37	−21
Latvia	5.47	5.79	6	1.83	1.31	−28	10.72	11.17	4
Lithuania	6.35	6.85	8	1.89	2.03	7	12.60	14.14	12
Luxembourg	4.99	5.21	4	1.70	1.15	−32	8.51	8.97	5
Macedonia	1.75	1.67	−5	0.88	0.61	−31	3.10	2.85	−8
Malta	2.41	3.24	34	0.76	0.53	−30	4.20	3.58	−15
The Netherlands	7.13	7.71	8	1.64	1.49	−9	10.44	10.88	4
Norway	3.01	3.23	7	0.49	0.57	16	3.64	4.22	16
Poland	4.92	4.40	−11	1.43	1.14	−20	9.16	7.79	−15
Portugal	5.51	5.35	−3	3.29	2.99	−9	10.94	10.95	0
Republic of Moldova	3.06	3.14	3	1.04	0.64	−38	6.02	5.66	−6
Romania	3.01	3.57	19	1.44	1.48	3	6.54	7.79	19
Russian Federation	6.57	6.07	−8	1.45	1.16	−20	11.54	10.53	−9
Slovakia	7.23	6.48	−10	3.68	2.17	−41	15.43	13.69	−11
Slovenia	4.91	4.40	−10	2.05	1.13	−45	8.17	7.51	−8
Spain	4.82	4.13	−14	1.66	1.21	−27	8.88	7.26	−18
Sweden	3.09	3.08	−0	0.52	0.55	6	4.24	4.26	0
Switzerland	4.83	4.56	−6	1.04	0.72	−31	7.28	6.67	−8
Ukraine (2005–2006, 2008–2009)	4.85	4.45	−8	1.62	1.34	−17	9.99	9.44	−6
UK	8.71	8.71	0	1.92	1.74	−9	11.67	11.57	−1
UK, England and Wales	8.53	8.54	0	1.86	1.71	−8	11.35	11.25	−1
UK, Northern Ireland	7.80	8.28	6	2.62	1.83	−30	10.93	12.14	11
UK, Scotland	10.93	10.63	−3	2.33	2.02	−13	15.16	14.61	−4
EU (27)	5.34	4.99	−7	1.68	1.30	−23	9.03	8.25	−9

Persisting favorable trends in overall male esophageal cancer mortality rates are predicted up to 2015 (Figure 3): in the EU, the predicted age-standardized mortality rate is 4.46/100 000, corresponding to ~22 300 esophageal cancer deaths. The predicted rates are 4.24/100 000 for France, 4.17/100 000 for Germany, 1.67/100 000 for Italy, 3.14/100 000 for Poland, 3.52/100 000 for Spain and 8.51/100 000 for the UK. Among EU women, the predicted age-standardized mortality rate is 1.07/100 000, corresponding to ~7400 esophageal cancer deaths.

Among men (Figure 4), increasing EAC incidence trends were observed in most countries, while ESCC trends have been decreasing or stabilizing over the last few decades. In Denmark, the Netherlands, England and Scotland, the increases in male EAC trends were among the steepest observed, and the EAC incidence is now higher than that of the ESCC. In central and southern Europe, smaller rises in EAC were observed and ESCC remains the predominant histological type among men.

Trends were less stable among women (supplementary Figure S1, available at *Annals of Oncology* online), as very low histology-specific incidence rates were observed. ESCC was the predominant histological type among women in all registration areas considered and still presented increasing trends in Austria, Denmark, Estonia, Slovakia and Switzerland.

Table 2. Age-standardized (world population) mortality rates from esophageal cancer per 100 000 women (at all ages and truncated at 25–49 and 35–64 years) in selected European countries and in the European Union (EU) in the periods 2000–2004 and 2005–2009 (unless otherwise mentioned in parenthesis), and corresponding percent changes

	All ages			25–49 years			35–64 years		
	2000–2004	2005–2009	% change	2000–2004	2005–2009	% change	2000–2004	2005–2009	% change
Austria	0.65	0.61	−6	0.16	0.09	−44	1.02	0.93	−9
Belarus (2000–2003/2007–2009)	0.35	0.30	−14	0.14	0.08	−43	0.44	0.38	−14
Belgium (2003–2004)	1.46	1.32	−10	0.42	0.19	−55	2.47	1.93	−22
Bulgaria	0.48	0.39	−19	0.23	0.13	−43	0.70	0.62	−11
Croatia	0.64	0.61	−5	0.21	0.11	−48	0.84	0.71	−15
Czech Republic	0.60	0.64	7	0.24	0.10	−58	0.93	1.06	14
Denmark	1.91	1.71	−10	0.49	0.29	−41	2.49	2.40	−4
Estonia	0.48	0.43	−10	0.07	0.16	129	0.56	0.71	27
Finland	0.87	0.97	11	0.06	0.08	33	0.77	1.08	40
France	1.01	0.98	−3	0.34	0.24	−29	1.57	1.53	−3
Germany	1.00	1.04	4	0.25	0.23	−8	1.65	1.67	1
Greece	0.31	0.27	−13	0.09	0.07	−22	0.30	0.23	−23
Hungary	1.17	0.96	−18	0.64	0.45	−30	2.58	2.16	−16
Iceland	1.07	1.22	14	0.00	0.00	.	0.38	0.77	103
Ireland	3.16	2.84	−10	0.45	0.37	−18	3.14	2.57	−18
Italy (2000–2003/2006–2009)	0.56	0.47	−16	0.12	0.12	0	0.71	0.62	−13
Latvia	0.44	0.59	34	0.09	0.04	−56	0.62	0.88	42
Lithuania	0.50	0.65	30	0.15	0.28	87	0.74	1.15	55
Luxembourg	0.98	1.02	4	0.00	0.21	.	0.69	1.90	175
Macedonia	0.42	0.25	−40	0.10	0.05	−50	0.64	0.31	−52
Malta	0.41	0.84	105	0.00	0.00	.	0.41	0.73	78
The Netherlands	2.09	2.17	4	0.47	0.35	−26	2.83	2.91	3
Norway	0.86	0.81	−6	0.17	0.05	−71	1.14	1.13	−1
Poland	0.74	0.75	1	0.20	0.17	−15	1.08	1.15	6
Portugal	0.72	0.55	−24	0.15	0.13	−13	0.73	0.54	−26
Republic of Moldova	0.43	0.34	−21	0.16	0.11	−31	0.68	0.54	−21
Romania	0.41	0.46	12	0.17	0.17	0	0.60	0.81	35
Russian Federation	0.99	0.84	−15	0.19	0.17	−11	1.01	0.95	−6
Slovakia	0.62	0.59	−5	0.35	0.20	−43	1.15	0.98	−15
Slovenia	0.67	0.59	−12	0.10	0.10	0	0.52	1.00	92
Spain	0.47	0.48	2	0.21	0.16	−24	0.72	0.78	8
Sweden	0.94	0.89	−5	0.25	0.10	−60	1.16	1.14	−2
Switzerland	1.03	1.13	10	0.21	0.15	−29	1.44	1.52	6
Ukraine (2005–2006, 2008–2009)	0.39	0.31	−21	0.09	0.10	11	0.48	0.47	−2
UK	3.20	3.04	−5	0.49	0.46	−6	3.26	3.26	0
UK, England and Wales	3.12	2.96	−5	0.50	0.46	−8	3.20	3.20	0
UK, Northern Ireland	2.84	2.69	−5	0.30	0.37	23	2.92	3.06	5
UK, Scotland	4.04	3.97	−2	0.52	0.52	0	3.99	3.90	−2
EU (27)	1.12	1.09	−3	0.28	0.22	−21	1.51	1.51	0

Among men, most countries in northern and western Europe showed a higher proportion of EAC than any other histological type and presented the lowest values of the ESCC/EAC ratio, whereas in southern, central/eastern Europe the proportions of ESCC were generally higher (supplementary Figure S2 and Table S2, available at *Annals of Oncology* online). Among women (supplementary Figure S3 and Table S2, available at *Annals of Oncology* online), the proportion of ESCC incident cases was higher than that of EAC in all large countries. Central and eastern European countries showed the highest proportions of unspecified esophageal cancers in both sexes.

discussion

This updated analysis of esophageal cancer mortality trends in Europe confirms the long-term downward mortality rates observed for male esophageal cancer in several western countries, while in central European countries mortality trends were upwards until mid-1990s and started to stabilize or decline only over recent years. However, in some eastern and northern countries, male esophageal cancer mortality is still increasing. Mortality rates among European women remained comparatively low and showed stable or decreasing trends in some countries.

Regarding incidence, the EAC rates rose substantially among men in northern Europe and surpassed ESCC ones over the last decade, whereas ESCC remains the predominant histological type among European women and rates are still increasing in several countries. Such trends are unlikely to be attributable to a better classification of cases, as the unspecified esophageal cancer rates were low and did not appreciably decline in those countries. However, incidence trends must be interpreted with caution, since in some European countries incidence data had only a limited coverage of population.

Improvements in disease management may have somewhat influenced esophageal cancer mortality, as some increase in relative survival has been observed across Europe in the last few decades [13]. However, the heterogeneity in esophageal cancer incidence and mortality trends mostly reflects the differences in the exposure to the main determinants of EAC and ESCC cancer and their variations with time and across populations.

Alcohol consumption is associated with an increased risk of ESCC [14] but not of EAC [15], whereas tobacco smoking is a risk factor for both ESCC and EAC, the association being, however, stronger for ESCC [16, 17]. EAC is also associated with overweight/obesity and gastro-esophageal reflux disease [18], and it is inversely related to *Helicobacter pylori* infection [19]. Dietary aspects (i.e., low consumption of fruit and vegetables and high intake of meat, saturated fats and refined carbohydrates) are also related to esophageal cancer risk [20], and a non-negligible fraction of incident cases may be attributable to these factors [21, 22].

Trends and patterns in alcohol consumption have been largely heterogeneous across Europe, with widely debated rises in several Nordic and central European countries, Russia and the UK, and not so widely appreciated decreases in southern European countries [23]. Favorable trends observed in male mortality rates in countries from southern Europe followed the steady fall in alcohol consumption over the last few decades [23, 24], similarly to what has been observed for oral and pharyngeal cancers [25, 26]. Such favorable trends may also be due to changes in the composition of alcoholic beverages, including a reduction in acetaldehyde levels in most of these countries [27]. ESCC rates reflected the trends in alcohol consumption, decreasing in southern countries (e.g., France, Italy and Spain), and stabilizing in northern countries (e.g., Denmark and the UK), while EAC followed more consistently the trends in overweight/obesity, with more appreciable increases in northern Europe than in southern countries [28, 29].

Tobacco consumption has steadily declined in men from most European countries over the last few decades. However, changes in smoking have been less notable than those in alcohol drinking in southern Europe. Furthermore, alcohol and tobacco have a synergistic effect on esophageal cancer risk and the relative risks for combined exposures are one or two orders of magnitude greater than that of nonsmokers and nondrinkers [30]. Thus, limitation of one of these factors leads to the avoidance of a substantial proportion of cases on a population level [21].

Esophageal cancer trends in women are more difficult to interpret in terms of changes in exposure to risk factors, also on account of their much lower rates. Still, EAC was proportionally much less common than ESCC in women compared with men. This has long been recognized, but it is still surprising given that

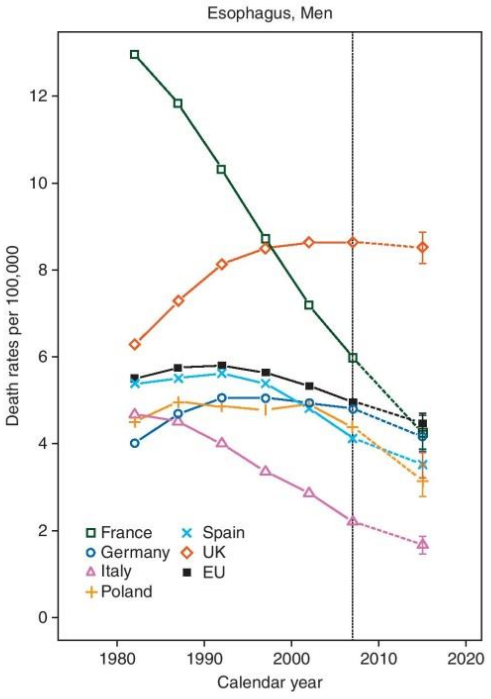

Figure 3. Trends in age-standardized (world population) mortality rates per 100 000 men for esophageal cancer in the European Union (EU) as a whole and selected European countries from 1980 to 2011, and predicted rates for 2015.

women drink and smoke less than men. A possible explanation is the lower frequency of abdominal obesity in women, with consequently less gastro-esophageal reflux [31]. Another reason may be that women use less frequently tight belts and wear dresses [32].

In conclusion, esophageal cancer mortality has been stabilizing or decreasing in most European countries, and it is expected to decrease further in the next few years. Among men, EAC is now the predominant histological type in northern countries, while ESCC remains the most common subtype in women.

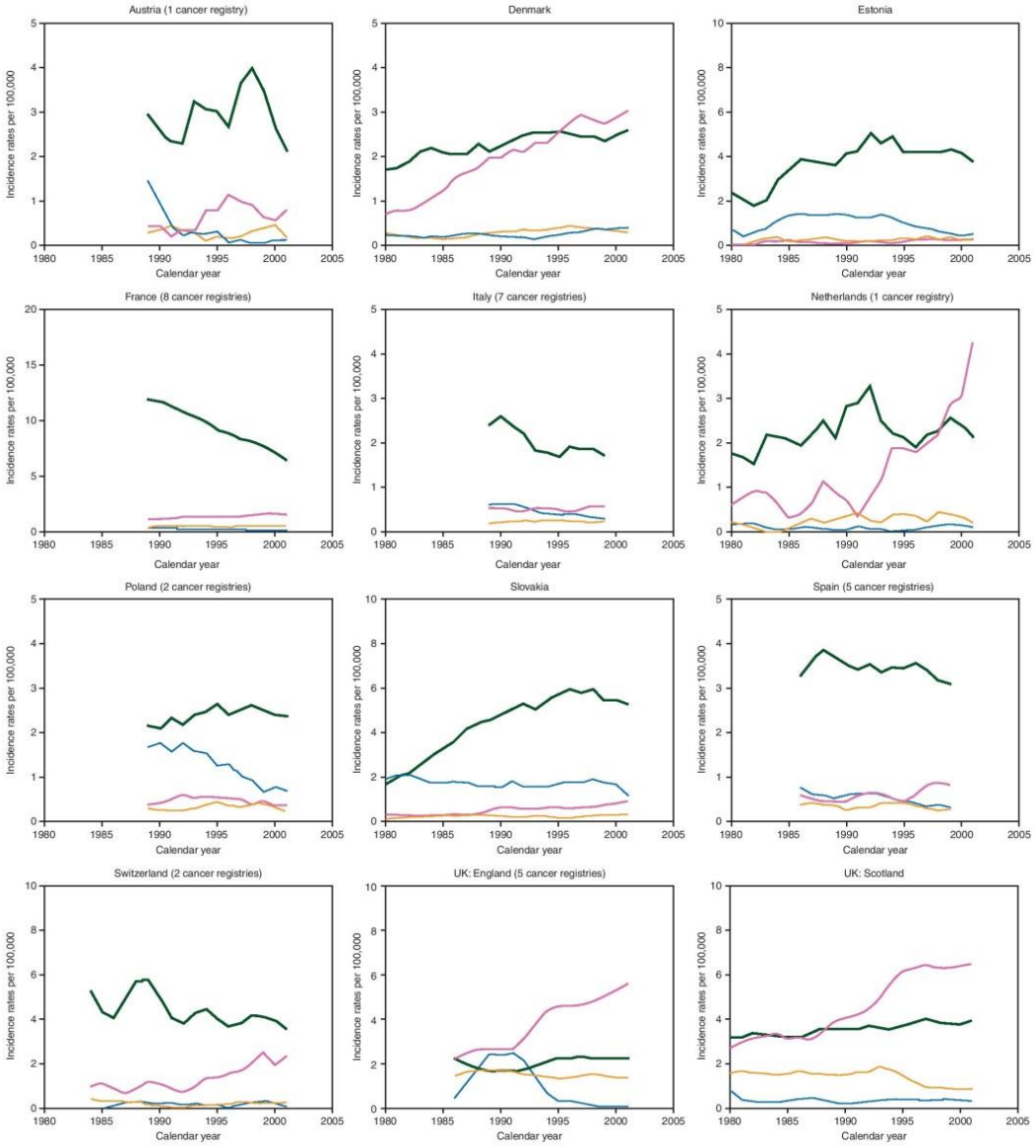

Figure 4. Trends in age-standardized (world population) incidence rates per 100 000 men for esophageal cancer by histological types in selected European countries, 1980–2002. —esophageal squamous cell carcinoma; —esophageal adenocarcinoma; —unspecified esophageal cancers; — other esophageal cancers.

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disclosure

The authors have declared no conflicts of interest.

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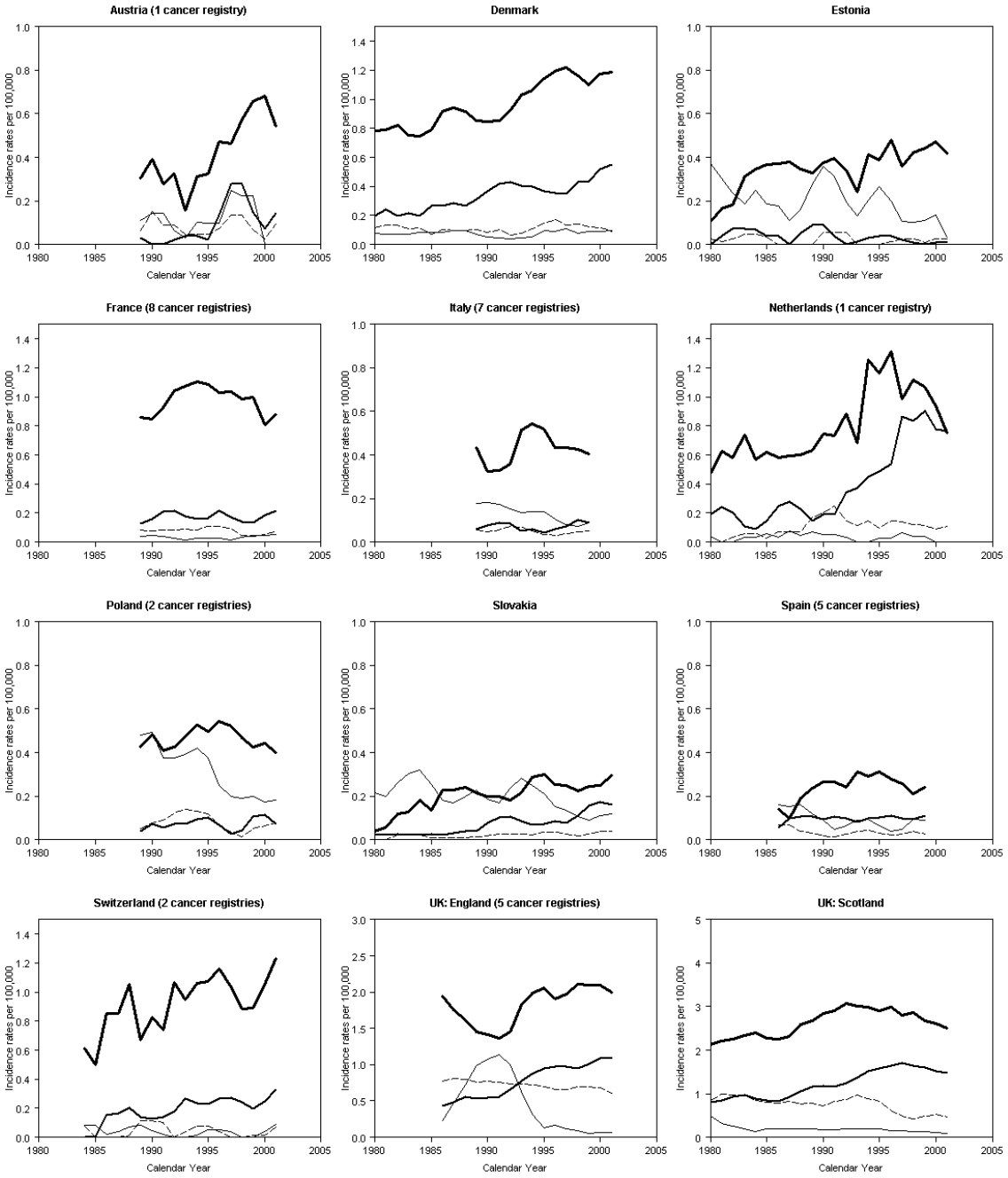
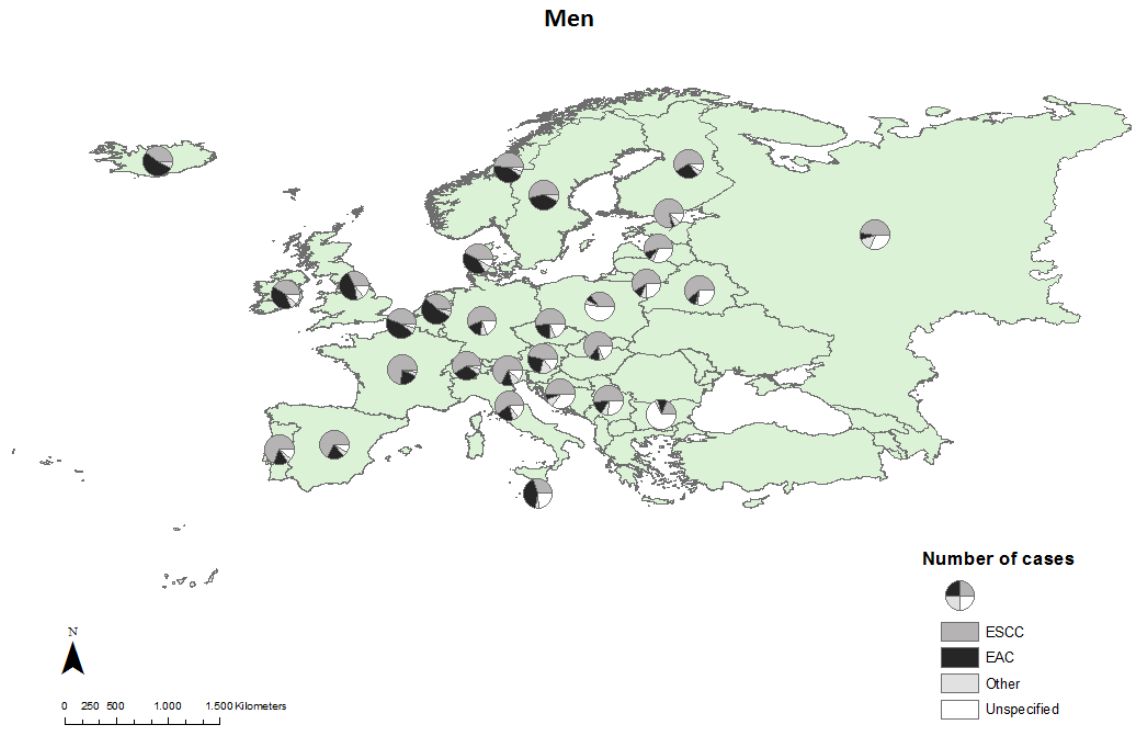
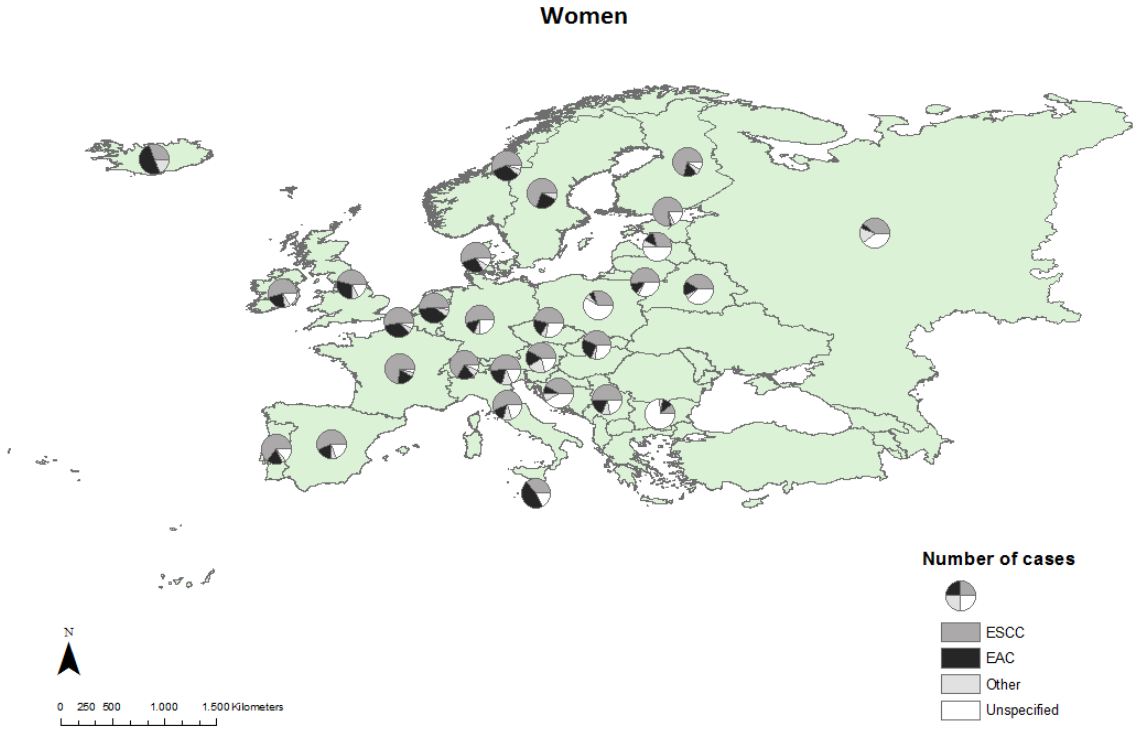


Supplementary Figure 1: Trends in age-standardized (world population) incidence rates per 100,000 women for esophageal cancer by histological types in selected European countries, 1980-2002.



Supplementary Figure 2: Proportion of cases of the four esophageal cancer subtypes, i.e., squamous cell carcinoma (ESCC), adenocarcinoma (EAC), other esophageal cancers and unspecified esophageal cancers, among men, across Europe.



Supplementary Figure 3: Proportion of cases of the four esophageal cancer subtypes, i.e., squamous cell carcinoma (ESCC), adenocarcinoma (EAC), other esophageal cancers and unspecified esophageal cancers, among women, across Europe.

Supplementary Table S1: Joinpoint analysis for esophageal cancer mortality in men and women (at all ages and 25-49 and 35-64 years) for the European Union and selected European countries, from 1980 to 2011.

		Men									*Women*								
Country	***Age group***	***Years***	***APC 1***	***Years***	***APC 2***	***Years***	***APC 3***	***Years***	***APC 4***	***AAPC***	***Years***	***APC 1***	***Years***	***APC 2***	***Years***	***APC 3***	***Years***	***APC 4***	***AAPC***
Austria	All ages	1980-2011	-0.1							-0.1	1980-1993	-0.6	1993-1999	7.5	1999-2011	-2[a]			0.4
	25-49 years	1980-2011	-1.6[a]							-1.6[a]	1980-2011	0.2							0.2
	35-64 years	1980-2007	0.4	2007-2011	-6.1					-0.5	1980-2003	3.1[a]	2003-2011	-4.8					1
Bulgaria	All ages	1980-1988	7.6[a]	1988-1991	31.4	1991-2002	-6.5[a]	2002-2011	2.2	2.8	1980-1986	1.4	1986-1991	33.6[a]	1991-2000	-12.4[a]	2000-2011	-1.8	0.5
	25-49 years	1980-1995	11.5[a]	1995-2001	-16.4[a]	2001-2011	1.8			2.4	1980-1991	23.8[a]	1991-2011	-7.6[a]					2.5
	35-64 years	1980-1991	16.4[a]	1991-2011	-2.8[a]					3.7[a]	1980-1991	25.8[a]	1991-2000	-13.1[a]	2000-2011	0.4			4.3
Czech Republic	All ages	1986-1995	4[a]	1995-2011	-0.8[a]					0.9[a]	1986-2011	1.4[a]							1.4[a]
	25-49 years	1986-1994	7.2[a]	1994-2011	-4.7[a]					-1.1	1986-2011	1.8							1.8
	35-64 years	1986-1993	7.3[a]	1993-2011	-1[a]					1.3[a]	1986-2011	3.9[a]							3.9[a]
Denmark	All ages	1980-2002	2.6[a]	2002-2008	-5.4[a]	2008-2011	5.5			1.3[a]	1980-2005	2.2[a]	2005-2011	-6.4[a]					0.5
	25-49 years	1980-2000	3.5[a]	2000-2011	-6.6[a]					-0.2	1980-2011	0.6							0.6
	35-64 years	1980-2000	2.9[a]	2000-2011	-3.3[a]					0.6	1980-2006	2[a]	2006-2011	-9.4					0.1
Finland	All ages	1980-2011	-0.2							-0.2	1980-2001	-4.4[a]	2001-2011	0.8					-2.8[a]
	25-49 years	1980-2011	1.5							1.5	1980-2011	-0.8							-0.8
	35-64 years	1980-2011	1.3[a]							1.3[a]	1980-2011	-1.8[a]							-1.8[a]
France	All ages	1980-1989	-1.6[a]	1989-2009	-3.5[a]					-3[a]	1980-2009	-0.1							-0.1
	25-49 years	1980-2000	-2.4[a]	2000-2009	-10.1[a]					-4.9[a]	1980-2000	1.5[a]	2000-2009	-6[a]					-0.9
	35-64 years	1980-1989	-1.4[a]	1989-2009	-4.1[a]					-3.3[a]	1980-2009	0							0
Germany	All ages	1980-1991	2.9[a]	1991-2011	-0.5[a]					0.7[a]	1980-1985	-0.3	1985-1995	3[a]	1995-2011	0.7[a]			1.3[a]
	25-49 years	1980-1991	3.5[a]	1991-2011	-3.9[a]					-1.4[a]	1980-1993	5.8[a]	1993-2011	-2.9[a]					0.6
	35-64 years	1980-1985	7.2[a]	1985-1992	3[a]	1992-2011	-1.6[a]			0.8[a]	1980-1993	4.8[a]	1993-2008	1.3[a]	2008-2011	-5.1			2.1[a]
Greece	All ages	1980-1992	-2.5[a]	1992-2010	-0.1					-1.1[a]	1980-2010	-2.6[a]							-2.6[a]
	25-49 years	1980-2010	0.1							0.1	1980-2010	-2.7[a]							-2.7[a]
	35-64 years	1980-1992	-3.7[a]	1992-2010	2[a]					-0.3	1980-2010	-2.4[a]							-2.4[a]
Hungary	All ages	1980-1990	5.9[a]	1990-1997	3.1[a]	1997-2011	-2.7[a]			1.3[a]	1980-2000	4.5[a]	2000-2011	-1.2					2.4[a]
	25-49 years	1980-1995	6.9[a]	1995-2003	-4[a]	2003-2011	-10.8[a]			-0.8	1980-1998	6[a]	1998-2011	-4.4					1.5
	35-64 years	1980-1990	7.7[a]	1990-1997	3.5[a]	1997-2011	-3.3[a]			1.7[a]	1980-2000	6.2[a]	2000-2011	-1.5					3.4[a]
Ireland	All ages	1980-1994	2.3[a]	1994-2010	-0.7					0.7[a]	1980-2010	-1.3[a]							-1.3[a]
	25-49 years	1980-2010	0.2							0.2	1980-2010	-1.6							-1.6
	35-64 years	1980-2010	0							0	1980-2010	-2.5[a]							-2.5[a]
Italy	All ages	1980-1986	0.2	1986-2001	-3[a]	2001-2006	-5.9	2006-2010	0	-2.5[a]	1980-2010	-1.9[a]							-1.9[a]
	25-49 years	1980-1986	0.5	1986-2010	-4.6[a]					-3.6[a]	1980-2010	-1.6[a]							-1.6[a]
	35-64 years	1980-1987	1	1987-2008	-4.1[a]	2008-2010	3.1			-2.5[a]	1980-2010	-1.3[a]							-1.3[a]
Latvia	All ages	1980-2010	1.6[a]							1.6[a]	1980-1992	4.3[a]	1992-1995	-20.5	1995-2010	3.5[a]			1.1
	25-49 years	1980-2010	0.3							0.3	1980-2010	-0.5							-0.5
	35-64 years	1980-1989	7.4[a]	1989-2010	0.7					2.7[a]	1980-2010	1.2							1.2
Lithuania	All ages	1981-2010	2.3[a]							2.3[a]	1981-2010	1.3[a]							1.3[a]
	25-49 years	1981-2010	0.1							0.1	1981-2010	2.5							2.5
	35-64 years	1981-1990	7.5[a]	1990-2010	1.5[a]					3.3[a]	1981-2010	1.8[a]							1.8[a]
Netherlands	All ages	1980-1995	4.5[a]	1995-2011	1.4[a]					2.8[a]	1980-1994	4[a]	1994-2011	0.8[a]					2.2[a]
	25-49 years	1980-1992	10.6[a]	1992-2011	-0.5					3.7[a]	1980-1996	5.9[a]	1996-2011	-4.9[a]					0.5

		Men									Women								
Country	***Age group***	***Years***	***APC 1***	***Years***	***APC 2***	***Years***	***APC 3***	***Years***	***APC 4***	***AAPC***	***Years***	***APC 1***	***Years***	***APC 2***	***Years***	***APC 3***	***Years***	***APC 4***	***AAPC***
	35-64 years	1980-1992	6.7[a]	1992-2011	1.6[a]					3.5[a]	1980-1995	6.3[a]	1995-2011	0.3					3.2[a]
Norway	All ages	1980-2011	1[a]							1[a]	1980-2011	1.4[a]							1.4[a]
	25-49 years	1980-2011	0.7							0.7	1980-2011	-0.6							-0.6
	35-64 years	1980-1989	5.6[a]	1989-2011	-0.3					1.4	1980-2011	2.3[a]							2.3[a]
Poland	All ages	1980-1983	7[a]	1983-2004	0	2004-2011	-3.2[a]			-0.1	1980-2011	-0.5[a]							-0.5[a]
	25-49 years	1980-1991	2.2	1991-2011	-3.2[a]					-1.3[a]	1980-2011	-0.5							-0.5
	35-64 years	1980-1983	12.1[a]	1983-2002	0.5	2002-2011	-3.6[a]			0.3	1980-2011	0.5[a]							0.5[a]
Portugal	All ages	1980-2011	-0.3[a]							-0.3[a]	1980-2011	-4[a]							-4[a]
	25-49 years	1980-2005	2.9[a]	2005-2011	-5.7					1.2	1980-2011	-4.7[a]							-4.7[a]
	35-64 years	1980-2011	0.7[a]							0.7[a]	1980-2011	-4.1[a]							-4.1[a]
Romania	All ages	1980-1990	1.1	1990-1993	10	1993-2011	3.1[a]			3.1[a]	1980-2011	0.3							0.3
	25-49 years	1980-1999	6.3[a]	1999-2011	-0.3					3.7[a]	1980-2011	0.1							0.1
	35-64 years	1980-2005	4.8[a]	2005-2011	0.4					3.9[a]	1980-2011	0.8[a]							0.8[a]
Russian Federation	All ages	1980-1982	-2	1982-1992	1.6[a]	1992-2000	-3.4[a]	2000-2010	-1.4[a]	-1[a]	1980-1993	-2.8[a]	1993-1996	-7.2	1996-2010	-3.4[a]			-3.5[a]
	25-49 years	1980-1990	3.7[a]	1990-2010	-4.7[a]					-1.9[a]	1980-2010	-2.8[a]							-2.8[a]
	35-64 years	1980-1992	2.7[a]	1992-1999	-4.1[a]	1999-2010	-1.7[a]			-0.5[a]	1980-1992	-2.5[a]	1992-1997	-8.6[a]	1997-2010	-1.7[a]			-3.2[a]
Spain	All ages	1980-1995	0.4[a]	1995-2011	-2.5[a]					-1.1[a]	1980-1995	-3.7[a]	1995-2011	0.1					-1.7[a]
	25-49 years	1980-1995	0.9	1995-2011	-5.8[a]					-2.6[a]	1980-2011	0.1							0.1
	35-64 years	1980-1995	1.3[a]	1995-2011	-3.5[a]					-1.2[a]	1980-2011	0.4							0.4
Sweden	All ages	1980-2010	0.3							0.3	1980-2010	0.6[a]							0.6[a]
	25-49 years	1980-2010	0							0	1980-2010	1.5							1.5
	35-64 years	1980-2010	0.5[a]							0.5[a]	1980-2010	1.4[a]							1.4[a]
Switzerland	All ages	1980-2010	-1.2[a]							-1.2[a]	1980-2010	0.4							0.4
	25-49 years	1980-1994	1.7	1994-2010	-6.6[a]					-2.8[a]	1980-2010	-1.4							-1.4
	35-64 years	1980-2010	-1.3[a]							-1.3[a]	1980-2010	1.1[a]							1.1[a]
Ukraine	All ages	1981-1992	4.7[a]	1992-2003	-2.7[a]	2003-2011	-0.5			0.5[a]	1981-1992	-0.4	1992-2011	-3.8[a]					-2.5[a]
	25-49 years	1981-1990	6.7[a]	1990-2011	-3.6[a]					-0.6	1981-2011	-2[a]							-2[a]
	35-64 years	1981-1992	5.7[a]	1992-2002	-2.8[a]	2002-2011	-0.5			0.9[a]	1981-2011	-1.7[a]							-1.7[a]
United Kingdom	All ages	1980-1994	2.5[a]	1994-2010	0.1					1.2[a]	1980-1995	1.1[a]	1995-2010	-1[a]					0
	25-49 years	1980-1995	2.4[a]	1995-2010	-0.7					0.8[a]	1980-2010	-1[a]							-1[a]
	35-64 years	1980-1994	2.2[a]	1994-2010	0.1					1.1[a]	1980-1992	0.4	1992-2010	-0.9[a]					-0.4
European Union (27)	All ages	1980-1985	1.3[a]	1985-1994	0.2	1994-2009	-1.2[a]			-0.3[a]	1980-1995	0.3[a]	1995-2009	-0.6[a]					-0.2[a]
	25-49 years	1980-1985	2.3[a]	1985-1994	0.8[a]	1994-2002	-2.5[a]	2002-2009	-5.4[a]	-1.4[a]	1980-1996	1.9[a]	1996-2009	-2.9[a]					-0.2
	35-64 years	1980-1990	1.5[a]	1990-2003	-1[a]	2003-2009	-2.2[a]			-0.4[a]	1980-2009	0.5[a]							0.5[a]

[a] significantly different from 0 ($p < 0.05$)

APC, estimated annual percent change

AAPC, estimated average annual percent change

Supplementary Table S2: Number of esophageal cancer incident cases in men and women, by histological type, and age-standardized rate ratio ESCC/EAC, by European country with available data in the Cancer Incidence in Five Continents volume IX (national data are provided unless if otherwise specified).

Country	Men					Women				
	ESCC	EAC	Other	Unspecified	ESCC/EAC	ESCC	EAC	Other	Unspecified	ESCC/EAC
Austria	632	339	164	162	2.0	141	62	66	71	2.5
Belarus	1109	158	43	432	7.2	85	35	9	80	2.1
Belgium [a]	698	754	101	83	1.8	255	163	30	33	1.0
Bulgaria	146	78	19	459	1.9	22	23	8	152	1.0
Croatia	495	55	88	305	9.1	90	17	18	88	4.8
Czech Republic	929	420	117	314	2.2	150	61	19	89	2.7
Denmark	503	610	97	119	0.9	284	150	33	51	2.2
Estonia	175	11	15	23	16.8	37	1	2	8	41.0
Finland	362	243	38	57	1.5	281	61	23	34	4.3
France [b]	2178	581	136	64	6.5	386	92	26	23	4.3
Germany [c]	2396	791	270	762	4.4	608	178	71	285	3.3
Iceland	21	26	2	0	0.7	5	8	3	0	0.6
Ireland	295	489	69	88	0.6	329	132	39	97	2.7
Italy [d]	1680	560	200	345	4.7	503	127	83	178	3.5
Latvia	259	37	16	123	7.2	23	10	5	38	2.0
Lithuania	429	59	45	174	7.5	53	13	4	33	4.6
Malta	11	16	2	10	0.7	4	5	0	2	1.0
Norway	277	260	38	25	1.2	140	85	16	11	2.0
Poland [e]	187	28	25	251	5.9	40	9	7	79	6.8
Portugal [f]	915	199	71	133	3.3	197	57	12	43	5.3
Russia [g]	560	90	148	279	6.4	174	26	69	177	6.3
Serbia	283	83	35	148	3.6	83	31	14	37	3.1
Slovakia	847	121	52	233	7.2	56	32	6	34	2.0
Slovenia	268	39	28	36	7.1	47	19	10	17	3.2
Spain [h]	1416	403	111	151	3.2	168	56	17	59	4.3
Sweden	614	621	97	13	1.0	407	147	37	5	3.0
Switzerland [i]	402	243	38	23	4.4	144	43	17	12	1.9
Netherlands	1441	2523	268	74	0.6	903	720	135	38	1.6
United Kingdom [j]	4936	12169	1492	2622	1.9	6179	3801	1128	2206	0.4

ESCC: squamous cell carcinoma; EAC: esophageal adenocarcinoma

[a] Antwerp and Flanders

[b] Bas-Rhin, Calvados, Doubs, Haut-Rhin, Herault, Isere, Loire-Atlantique, Manche, Somme, Tarn, Vendee

[c] Brandenburg, Free State of Saxony, Hamburg, Mecklenburg-Western Pomerania, Munich, Northrhine-Westphalia: Munster, Saarland

[d] Biella, Brescia, Ferrara, Florence and Prato, Genoa, Macerata, Milan, Modena, Naples, North East Cancer Surveillance Network, Parma, Ragusa, Reggio Emilia, Romagna, Salerno, Sassari, Syracuse, Sondrio, Torino, Umbria, Varese, Veneto

[e] Cracow, Kielce, Warsaw

[f] Northern and Southern Regions

[g] St Petersburg

[h] Albacete, Asturias, Basque Country, Canary Islands, Cuenca, Girona, Granada, Murcia, Navarra, Tarragona, Zaragoza

[i] Geneva, Graubunden and Glarus, Neuchatel, St Gall-Appenzell, Ticino, Valais, Vaud

[j] East of England Region, England (Merseyside and Cheshire, North Western, Northern and Yorkshire, Oxford, South and Western, Thames, Trent, West Midlands), Northern Ireland, Scotland

Paper II

Castro C, Antunes L, Lunet N, Bento MJ.

CANCER INCIDENCE PREDICTIONS IN THE NORTH OF PORTUGAL: KEEPING POPULATION-BASED CANCER REGISTRATION UP TO DATE.

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Cancer incidence predictions in the North of Portugal: keeping population-based cancer registration up to date

Clara Castro[a,b,c], Luís Antunes[a], Nuno Lunet[b,c] and Maria José Bento[a]

Decision making towards cancer prevention and control requires monitoring of trends in cancer incidence and accurate estimation of its burden in different settings. We aimed to estimate the number of incident cases in northern Portugal for 2015 and 2020 (all cancers except nonmelanoma skin and for the 15 most frequent tumours). Cancer cases diagnosed in 1994–2009 were collected by the North Region Cancer Registry of Portugal (RORENO) and corresponding population figures were obtained from Statistics Portugal. JoinPoint regression was used to analyse incidence trends. Population projections until 2020 were derived by RORENO. Predictions were performed using the Poisson regression models proposed by Dyba and Hakulinen. The number of incident cases is expected to increase by 18.7% in 2015 and by 37.6% in 2020, with lower increments among men than among women. For most cancers considered, the number of cases will keep rising up to 2020, although decreasing trends of age-standardized rates are expected for some tumours. Cervix was the only cancer with a decreasing number of incident cases in the entire period. Thyroid and lung cancers were among those with the steepest increases in the number of incident cases expected for 2020, especially among women. In 2020, the top five cancers are expected to account for 82 and 62% of all cases diagnosed in men and women, respectively. This study contributes to a broader understanding of cancer burden in the north of Portugal and provides the basis for keeping population-based incidence estimates up to date. *European Journal of Cancer Prevention* **00:000–000**

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Keywords: cancer, incidence, Poisson regression, predictions

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Introduction

Cancer is a leading cause of morbidity and mortality worldwide, with ~14 million new cases and 8.2 million cancer-related deaths estimated in 2012 (Ferlay *et al.*, 2013a). Moreover, by 2020, the number of incident cases is expected to increase by over 20%, with over 17 million people being diagnosed with cancer that year. In Portugal, as in Europe as a whole, this increase is expected to be more modest (~9–10%), although large differences are expected according to the cancer site and geographical region.

Decision making in the context of cancer prevention and control efforts requires monitoring of trends in cancer incidence and accurate estimation of its burden. Projections taking into account the expected demographic changes in the population provide up-to-date results that overcome the inherent delay between the moment events occur and the time data become available for annual reporting (Ferlay *et al.*, 2013b).

The International Agency for Research on Cancer has published incidence and mortality predictions for countries in Europe since the 1980s (Parkin *et al.*, 1993; Pisani *et al.*, 1993). However, given the heterogeneity between, as well as within, countries, it is useful to provide more detailed information on cancer for specific regions, because prevention and control efforts may have to reflect the differences between populations from specific geographical regions within nations. The North Region Cancer Registry of Portugal (RORENO) is a population-based cancer registry that covers ~3.2 million people who live in the five districts constituting northern Portugal (Braga, Bragança, Porto, Viana do Castelo and Vila Real). It was established in 1988 on a legal framework (government decree 35/88 of January 16th) and publishes annual reports on cancer incidence and mortality/incidence ratios in the region; survival data have also been published in local and international studies such as EUROCARE-5 and CONCORD-2. Apart from the initial years of operation, in which completeness of registration is expected to be lower, the functioning and resources involved in cancer registration in the region have been fairly stable. Currently, the last year of available data is 2009. That year, the 15 most frequent cancers

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in the north of Portugal comprised over 80% of the total number of diagnosed cases in the region (RORENO, 2015). This study aimed to analyse incidence trends and to estimate the number of cases in northern Portugal for 2015 and 2020, for all cancers except nonmelanoma skin and for the 15 most frequent tumours in the region.

Methods

We analysed data referring to the cancer cases diagnosed between 1994 and 2009 in the north of Portugal, for the 15 most frequent tumours in the region in 2009, considering the number of cases in both sexes together and all cancers except nonmelanoma skin. The cancers/groups of cancer [10th edition of the International Classification of Diseases (World Health Organization, 1992)] individually considered were oesophagus (C15), stomach (C16), colorectum (C18–C21), pancreas (C25), lung (C33–C34), melanoma of the skin (C43), female breast (C50), cervix uteri (C53), corpus uteri (C54), prostate (C61), kidney (C64), bladder (C67), brain and central nervous system (C70–C72), thyroid (C73) and non-Hodgkin lymphoma (C82–C85, C96).

Cancer data were retrieved from RORENO, by year of diagnosis, sex and 5-year age groups. Corresponding population figures were obtained from Statistics Portugal.

Sex-specific incidence rates were computed for each 5-year age group and calendar period, and age-standardized rates were calculated by the direct method, using the European standard population for all ages. Poisson regression analysis was performed using JoinPoint software (SEER, Bethesda, Maryland, USA) to identify significant changes in incidence trends (allowing up to two joinpoints and fixing four as the minimum number of observations from a joinpoint to either end of the data). For each of the segments obtained in the best model, the estimated annual percent change (APC) was computed by fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable.

We used 3-year moving averages to represent sex-specific incidence trends in the number of cases and age-standardized incidence rates (ASIR) for each cancer site.

Predicted numbers of cases for the years 2015 and 2020 were derived using the linear (for increasing or stabilizing trends) or log-linear (for decreasing trends) Poisson regression models proposed by Dyba and Hakulinen (2000) and Hakulinen and Dyba (1994). In these models, incidence data by age group (0–34, 35–44, 45–54, 55–64, 65–74, 75–84 and $\geq$85 years) over the most recent time period identified by sex-specific and site-specific joinpoint models were used.

For prostate cancer, an alternative scenario was considered (please see footnote of Supplemental Fig. 1, Supplemental digital content 1, *http://links.lww.com/EJCP/A24*), assuming a pattern of variation in incidence rates similar to the one that was observed in other settings (Center *et al.*, 2012; Fontes *et al.*, 2013), where a steep increase due to prostate-specific antigen screening was followed by a decline and again a continued increase in rates in the most recent years.

Among women, an alternative scenario was considered for thyroid cancer (please see footnote of Supplemental Fig. 2, Supplemental digital content 2, *http://links.lww.com/EJCP/A25*), following the pattern observed in the USA (Li *et al.*, 2013; Davies and Welch, 2014), where rates are as high as in the north of Portugal, some of the highest in the world, and a marked but steady increase has been observed since the early/mid 1990s, with no steeper increase afterwards.

Age-specific numbers of cancer cases, ASIR and corresponding 95% prediction intervals were computed for 2015 and 2020 using the population predictions performed by RORENO; the latter were calculated assuming a constant fertility rate and modelling migration rates to accommodate the known population figures up to 2012 (central scenario). Two additional population projections were calculated, by assuming either an increasing (higher population growth scenario) or a decreasing (lower population growth scenario) fertility rate in the region, to include the 'central' prediction in a range of possible variability.

The RiskDiff (Valls *et al.*, 2009) tool was used to split the expected variation in the number of cases in 2009–2020 between changes in risk and in demography (population size and structure).

Statistical analyses were performed using Stata v.12 (StataCorp, 2011).

Results

For all cancers except nonmelanoma skin, a non-significant variation was observed in male incidence trends since 2005 (APC = 1.0), whereas there was a significant increase in women since 2000 (APC = 3.4) (Table 1). The number of incident cases registered is expected to increase, as compared with 2009, by 18.7% (13.3–24.0%) in 2015 and by 37.6% (29.2–45.9%) in 2020, with smaller increments in men. For 2020, over 20 000 new cancer cases are expected in the region (men: n = 10 236, ASIR = 500.8/100 000; women: n = 9820, ASIR = 422.4/100 000) (Fig. 1 and Table 2). The net changes in the number of cases between 2009 and 2020 were 2819 (35.6%) and 3092 (46.4%) cases, respectively, for men and women, which can be partitioned into 1822 (23.0%) and 2478 (37.2%) cases due to an increment in risk, and to 997 (12.6%) and 614 (9.2%) due to the changes in the population structure and size (Fig. 2).

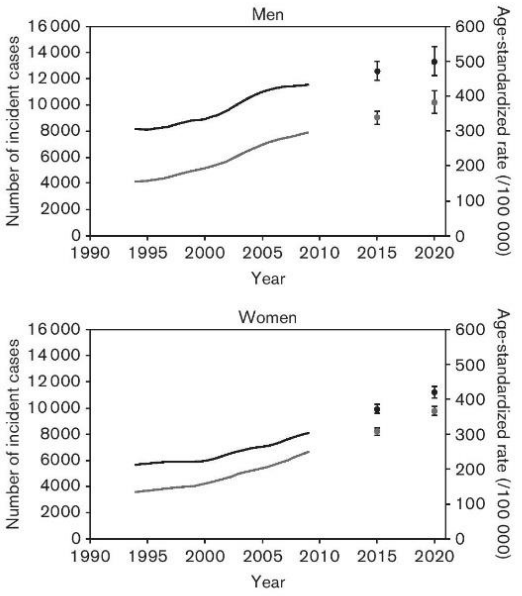
In the most recent years, statistically significant increases in ASIR were found for all cancer sites, except the

Table 1 Annual percent change and 95% confidence intervals in age-standardized (all ages, direct method, European standard population) incidence rates in the periods identified by joinpoint analysis, by cancer site and by sex, in 1994–2009

	Men						Women					
Cancer site (ICD-10)	Period 1	APC (95% CI)	Period 2	APC (95% CI)	Period 3	APC (95% CI)	Period 1	APC (95% CI)	Period 2	APC (95% CI)	Period 3	APC (95% CI)
All cancers (except skin nonmelanoma)	1994–2001	1.8 (1.1–2.4)	2001–2005	5.2 (3.1–7.3)	2005–2009	1.0 (−0.1 to 2.1)	1994–2000	0.8 (−0.4 to 2.1)	2000–2009	3.4 (2.9–4.0)		
Oesophagus (C15)	1994–2009	0.6 (−0.8 to 1.9)					1994–2009	−2.7 (−4.7 to −0.6)				
Stomach (C16)	1994–2009	−1.2 (−1.6 to −0.9)					1994–2009	−1.6 (−2.3 to −1.0)				
Colorectum (C18–C21)	1994–2001	2.1 (0.7–3.6)	2001–2009	4.6 (3.7–5.5)			1994–2009	2.4 (1.9–2.9)				
Pancreas (C25)	1994–2009	5.9 (3.4–8.5)					1994–2009	6.2 (3.1–9.5)				
Lung (C33–C34)	1994–2009	2.7 (2.0–3.4)					1994–2009	5.5 (4.2–6.9)				
Melanoma of the skin (C43)	1994–2009	6.3 (4.7–7.9)					1994–2009	5.3 (3.4–7.3)				
Female breast (C50)	NA	NA	NA	NA	NA	NA	1994–2009	3.5 (3.1–3.9)				
Cervix uteri (C53)	NA	NA	NA	NA	NA	NA	1994–2009	−2.6 (−3.4 to −1.8)				
Corpus uteri (C54)	NA	NA	NA	NA	NA	NA	1994–2001	−2.5 (−5.3 to 0.3)	2001–2009	4.6 (2.5–6.7)		
Prostate (C61)	1994–2006	6.1 (4.8–7.4)	2006–2009	−3.7 (−11.1 to 4.3)			NA	NA	NA	NA	NA	NA
Kidney (C64)	1994–2009	6.1 (4.9–7.3)					1994–2009	3.7 (2.0–5.5)				
Bladder (C67)	1994–2009	3.3 (2.6–3.9)					1994–1997	−9.1 (−18.1 to 1.0)	1997–2000	9.5 (−11.1 to 34.8)	2000–2009	1.0 (−0.6 to 2.6)
Brain and CNS (C70–C72)	1994–2009	2.6 (1.2–4.1)					1994–2009	3.0 (1.4–4.6)				
Thyroid (C73)	1994–2009	11.8 (9.5–14.1)					1994–2006	8.3 (7.1–9.6)	2006–2009	19.9 (12.7–27.4)		
Non-Hodgkin lymphoma (C82–C85, C96)	1994–2009	3.3 (2.4–4.1)					1994–2009	2.9 (1.7–4.0)				

APC, annual percent change; 95% CI, 95% confidence interval; CNS, central nervous system; NA, not applicable.

Fig. 1



Trends in 3-year moving averages of the number of cases and age-standardized (all ages, direct method, European standard population) incidence rates in 1994–2009 (in grey and black, respectively) and predictions for 2015 and 2020, for all cancers except nonmelanoma skin, by sex.

stomach (both sexes), oesophagus, cervix and bladder (in women) and prostate (Table 1). However, the number of incident cases is expected to keep rising up to 2020, for all cancers considered in this study, except cervix cancer among women, although with large heterogeneity in the magnitude of variation according to cancer site and sex (Supplemental Figures 1, Supplemental digital content 1, *http://links.lww.com/EJCP/A24* and 2, Supplemental digital content 2, *http://links.lww.com/EJCP/A25*, Supplemental Table 1, Supplemental digital content 3, *http://links.lww.com/EJCP/A26*). For tumours common to both sexes, the number of incident cases was and is expected to remain generally higher in men, except for melanoma of the skin and thyroid cancer (Table 2).

Although stomach cancer presented significant declining incidence rates in the region, for both sexes (men: APC = – 1.2; women: APC = – 1.6), there was a slight increase in the number of incident cases, which is expected to increase by 3.1 and 4.3% in 2020 for men and women, respectively. In men, stomach is projected to remain the fourth most frequent cancer site in 2015, but it is expected to be replaced by bladder cancer in 2020. The net change in the number of cases was mainly attributable to demographic changes (Fig. 2).

Among women, oesophageal cancer presented a similar behaviour to stomach cancer, with significantly decreasing rates (APC = – 2.7) but an increasing number of cases. However, rates in women for this cancer site are low, and oesophageal cancer is likely to remain as the 15th most common cancer in 2020.

Cervix was the only cancer site that presented decreasing trends in both the number of incident cases and ASIR (APC = – 2.6) between 1994 and 2009, and these are expected to hold in the future. The number of incident cases is expected to drop just over 18% by 2020 (22.5% decrease due to lower risk and 4.2% increase due to demographic changes), and cervix cancer will likely drop from the 9th to the 11th most frequent cancer in women.

A decreasing ASIR trend was observed for prostate cancer between 2006 and 2008, although a higher rate was already observed in 2009. Assuming that an upward trend will be observed in the next years, prostate cancer is expected to remain the most common cancer in men, accounting for over 29% of all cancers predicted for 2020 (Table 2).

Melanoma of the skin was more common in women, and sex differences are expected to hold up to 2020, although men presented a slightly higher APC in incidence rates than did women (6.3 vs. 5.3) during 1994–2009. Furthermore, the percentage change in the number of cases diagnosed between 2009 and 2020 is quite similar between sexes, at ~30%, mainly due to an increase in risk (by 18.3% among men and 24.8% among women) (Fig. 2).

The steepest ASIR increase in 1994–2009 was observed for thyroid cancer (APC = 11.8 among men; APC = 8.3 in 1994–2006 and APC = 19.9 in 2006–2009 among women), and the corresponding number of incident cases is expected to increase by over 30% for both sexes (from 140 and 788 cases in 2009 to 186 and 1055 cases in 2020, respectively, for men and women) (Table 2). The net increase in thyroid cancer cases among men was mainly attributable to an increased risk of developing cancer, whereas in women it was mostly due to the changes in population size and structure (Fig. 2).

During 1994–2009, for lung cancer, the APC for women was nearly twice as high as that observed in men (5.9 vs. 2.9); this translates into one of the largest projected percentage changes (69.4%) in the number of incident cases among women from 2009 to 2020 (Table 2).

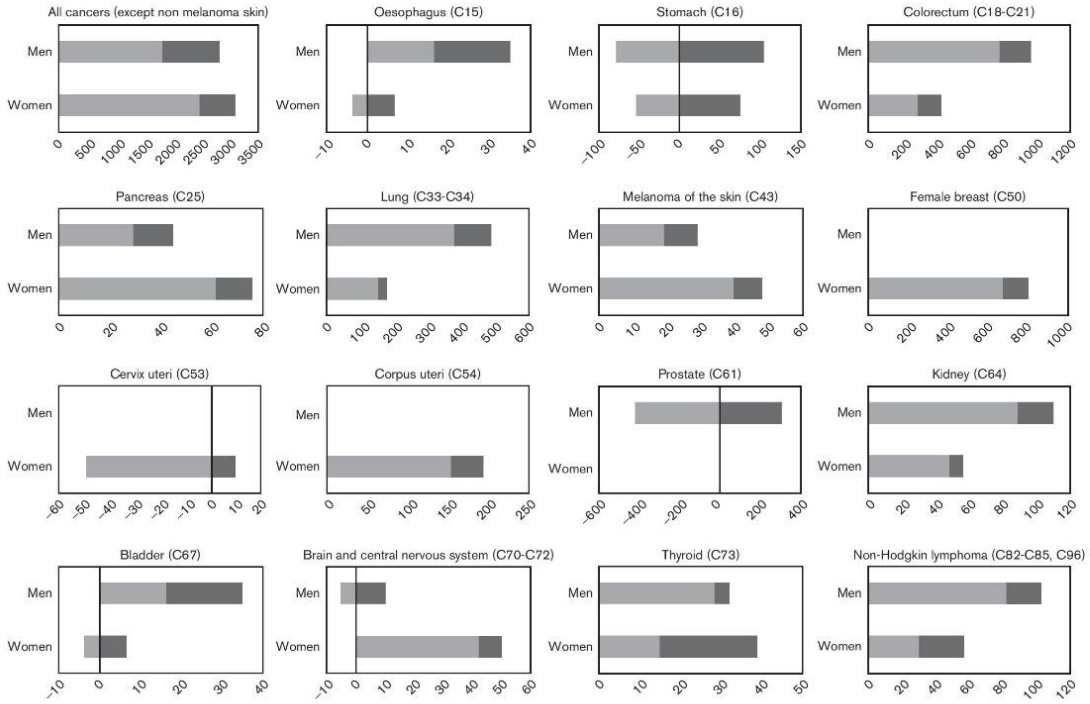
Among men, the five most frequent cancers (prostate, colorectum, lung, stomach and bladder) will account for a larger proportion of all cases diagnosed in a year, varying from 68% in 2009 to 82% in 2020. Among women, the top five cancers (breast, colorectum, stomach, thyroid and corpus uteri) accounted for nearly 65% of all female cancers diagnosed in 2009, and this proportion is expected to remain relatively stable up to 2020.

Table 2 Number of cases registered in 2009 and predictions for 2015 and 2020, and corresponding percentage changes, by cancer site and by sex, according to a central scenario of a stable fertility rate at 1.28, and the range of variability in predictions for 2020, calculated using scenarios of lower and higher population growth

	Men						Women					
Cancer site (ICD-10)	2009	2015	2020	Lower–higher estimates[a] 2020	% Change 2009–2015	% Change 2009–2020	Lower–higher % change 2009–2020	2009	2015	2020	Lower–higher estimates[a] 2020	% Change 2009–2015	% Change 2009–2020	Lower–higher % change 2009–2020
All cancers (except skin nonmelanoma)	7916	9057	10 236	10 161–10 372	14.4	29.3	28.4–31.0	6663	8243	9820	9775–9944	23.7	47.4	46.7–49.2
Oesophagus (C15)	168	186	202	200–203	10.7	20.2	19.0–20.8	31	32	32	32–33	3.2	3.2	3.2–6.5
Stomach (C16)	721	729	743	734–755	1.1	3.1	1.8–4.7	493	497	514	514–526	0.8	4.3	4.3–6.7
Colorectum (C18–C21)	1443	1939	2421	2406–2459	34.4	67.8	66.7–70.4	1024	1234	1464	1461–1491	20.5	43.0	42.7–45.6
Pancreas (C25)	123	141	175	174–178	14.6	42.3	41.5–44.7	99	135	170	169–173	36.4	71.7	70.7–74.7
Lung (C33–C34)	909	1151	1360	1351–1378	26.6	49.6	48.6–51.6	248	338	420	418–426	36.3	69.4	68.5–71.8
Melanoma of the skin (C43)	106	116	141	140–143	9.4	33.0	32.1–34.9	160	176	212	210–214	10.0	32.5	31.3–33.8
Female breast (C50)	NA	NA	NA	NA	NA	NA	NA	1743	2177	2541	2526–2561	24.9	45.8	44.9–46.9
Cervix uteri (C53)	NA	NA	NA	NA	NA	NA	NA	220	195	179	178–181	−11.4	−18.6	−19.1 to −17.7
Corpus uteri (C54)	NA	NA	NA	NA	NA	NA	NA	299	398	501	500–507	33.1	67.6	67.2–69.6
Prostate (C61)	1733	2351	3016	3000–3058	35.7	74.0	73.1–76.5	NA	NA	NA	NA	NA	NA	NA
Kidney (C64)	198	248	307	304–310	25.3	55.1	53.5–56.6	91	116	138	137–139	27.5	51.6	50.5–52.7
Bladder (C67)	580	724	873	869–889	24.8	50.5	49.8–53.3	140	168	194	193–198	20.0	38.6	37.9–41.4
Brain and CNS (C70–C72)	157	153	177	175–179	−2.5	12.7	11.5–14.0	104	133	155	154–156	27.9	49.0	48.1–50.0
Thyroid (C73)	140	149	186	183–187	6.4	32.9	30.7–33.6	788	934	1055	1048–1058	18.5	33.9	33.0–34.3
Non-Hodgkin lymphoma (C82–C85, C96)	265	305	356	353–360	15.1	34.3	33.2–35.8	230	250	292	290–295	8.7	27.0	26.1–28.3

CNS, central nervous system; NA, not applicable.
[a]Lower scenario of population growth; decreasing fertility rate, from 1.28 in 2009 to 1.24 in 2020. Higher scenario of population growth: increasing fertility rate, from 1.28 in 2009 to 1.32 in 2020 (Instituto Nacional de Estatística, 2014b).

Fig. 2



Variation in the number of cancer cases between 2009 and 2020, due to changes in the risk of developing the disease (light grey) or in demographic factors (dark grey), by cancer site and by sex.

Discussion

Up to 2020, the number of incident cases of cancer in northern Portugal is expected to increase, by ~30% in men (from 7916 in 2009 to 10 236 in 2020) and by nearly 50% in women (from 6663 in 2009 to 9820 in 2020). Among the most frequent cancers in the region, stomach (both sexes) and oesophageal and cervix (in women) cancers were the only ones presenting a significant decline in ASIR between 1994 and 2009, and cervix was the only one with a decreasing number of incident cases in that entire period. For all other sites, except the bladder (in women) and prostate (in men), a significantly increasing ASIR trend was found in the most recent years. Thyroid and lung cancers were among those with the steepest increases in the number of incident cases expected for 2020, especially among women.

Timeliness and completeness of case ascertainment remain the most important indicators of data quality in a cancer registry, and there must be a trade-off between these indicators, because registries often delay the dissemination of results to achieve higher completeness. A recent assessment of the quality of data from cancer registries in Europe concluded that the median latency for completion of incidence ascertainment was 18 months, and additional time required for dissemination was in the order of 3–6 months, with wide variations (Zanetti *et al.*, 2015). Although RORENO has not attained this timeliness, a quantitative evaluation of case ascertainment has yielded high levels of completeness for gastric cancer [a cancer of poor prognosis (De Angelis *et al.*, 2014; Allemani *et al.*, 2015)] and concluded that no meaningful improvements in completeness could be expected after 3 years since diagnosis, which may be considered, in this context, a minimum lag to be respected between diagnosis and the publication of valid incidence estimates (Castro *et al.*, 2012). As some delay is necessary in the publication of results from population-based cancer registries, short-term predictions based on the extrapolation of historical trends may provide valid up-to-date figures to support cancer prevention and control efforts (Ferlay *et al.*, 2013b). Unlike the expected long-term estimates, for short-term predictions, the naive assumption that the recent trends will not change meaningfully in the next few years holds true for most cancers. The exception would be the evidence of

variation in the exposure to cancer determinants between the most recent trends and those expected in the short term but not yet observable. However, as the lag times for the relation between most exposures and cancer are relatively long, it is unlikely that recent trends in the frequency of cancer determinants will influence the incidence estimates for the next decade. In contrast, contemporary changes in the access and use of cancer screening are expected to have an important impact on cancer incidence rates, which is not captured in historical trends but may be necessary to incorporate in data analysis to provide accurate predictions.

Tobacco use is the single greatest avoidable risk factor for cancer mortality worldwide, causing an estimated 22% of cancer-related deaths per year (World Health Organization, 2011). It is a risk factor for many types of cancer, including cancers of the lung, kidney, bladder, pancreas, stomach and cervix (Araújo *et al.*, 2011). About 80% of the worldwide lung cancer burden in men and at least 50% of the burden in women can be attributed to smoking alone (Ezzati *et al.*, 2005). In Portugal, the prevalence of smoking increased among women, especially in those aged 31–50 and 51–70 years (from 4.6 and 0.1% in 1988 to 16.4 and 4.5% in 2008, respectively) and decreased among men, with the steepest declines in those aged up to 30 years (from 41.8% in 1988 to 28.8% in 2008) and those aged at least 71 years (from 15.1% in 1988 to 4.6% in 2008) (Carreira *et al.*, 2012a). This is the most likely cause of a more marked increase in lung cancer rates among women than among men, although the latter were still showing a significant increase up to 2009, reflecting the long time lag between exposure and outcome (IARC, 2004).

There is a link between overweight and obesity and many types of cancer such as colorectum, breast, endometrium and kidney (World Health Organization, 2011), and in Portugal the increasing prevalence of overweight and obesity (from 51.9 to 55.1% among men and from 43.5 to 47.0% among women, between 1998 and 2005) is very likely an important contributor to current and future cancer incidence rates (Carreira *et al.*, 2012b).

Regarding gastric cancer, the trends observed in this study were in accordance with the worldwide steady decline of incidence and mortality rates over the last five decades (Ferro *et al.*, 2014). This decline has been mainly attributed to an increase in socioeconomic status, namely through improved food preservation practices and reduction in the frequency of *Helicobacter pylori* infection (Howson *et al.*, 1986; Parkin *et al.*, 2001). As evidence supports a nondecreasing trend in *H. pylori* infection in the Portuguese population (Lunet, 2011; Peleteiro *et al.*, 2014), the above-mentioned factors may have had a larger impact on the decreasing gastric ASIR obtained in the region in the last decades and projected for the near future.

Observed trends for thyroid cancer are also in accordance with worldwide estimates, which depict a steep increase in incidence, especially in women (Li *et al.*, 2013; Vigneri *et al.*, 2015). The upward trends in thyroid cancer incidence have been mainly attributed to improved ascertainment and diagnosis, and largely reflect overdiagnosis of indolent disease – that is, small papillary carcinomas (Vigneri *et al.*, 2015). Some countries have also detected increasing incidence rates for larger tumours but not for follicular carcinomas (Li *et al.*, 2013; Davies and Welch, 2014); therefore, it would be necessary to evaluate both histology-specific and tumour size-specific trends of thyroid cancer in northern Portugal to understand the extent to which the observed increasing rates reflect overdiagnosis.

In Portugal, organized screening programmes are planned and implemented independently in each region (North, Centre, Lisboa and Vale do Tejo, Alentejo and Algarve) by the corresponding Regional Health Administration, which causes inequalities in the access to screening across geographical areas (Parkin *et al.*, 2001; Bastos *et al.*, 2010). For colorectal cancer, there was no organized screening programme in Portugal up to 2009, despite the European Council Recommendation (2003/878/EC) to perform faecal occult blood tests in both men and women aged 50–74 years (Bastos *et al.*, 2010; Pinto *et al.*, 2010). The overall increasing ASIR observed for colorectal cancer may thus be attributable not to organized but to opportunistic screening – especially by endoscopic methods – as well as to changes in the exposure to risk factors. In northern Portugal, the breast cancer screening programme started in 1999, targeting women aged 45–69 (Bastos *et al.*, 2010; Bento *et al.*, 2014), but only 12.5% of the eligible population was covered in 2009, with a participation rate of 60.6% (ARS-Norte, 2010), which may explain the steady increase in the number of incident cases and ASIR observed in our study. For cervix cancer, a pilot programme was started in northern Portugal in 2009 (ARS-Norte, 2010); however, a large proportion of the population undergoes opportunistic screening (Alves *et al.*, 2009; Oliveira *et al.*, 2014), which likely contributed to the detection of premalignant diseases and a consequent decrease in the risk of cervix cancer.

Predicting cancer incidence largely depends on the projections of the resident population. We assessed this point by providing a range of variability in the number of predicted cases for 2015 and 2020 (using different scenarios for the evolution of population growth in the region, assuming increasing or decreasing fertility rates, in addition to stable fertility) and by evaluating the contribution of demographic changes to the expected number of cases. The differences in the percentage of changes obtained for 2009–2020 between the two alternative scenarios did not exceed 4%. However, the true impact of the current Portuguese context of emigration, low birth and ageing population (Instituto Nacional de

Estatística, 2014a) on the estimates provided in this work can only be assessed in future studies providing a comparison between predicted and observed numbers of cancer cases and rates.

The major strength of this study is the provision of up-to date figures for cancer control by using data on the most frequent cancer sites registered in a relatively young population-based cancer registry. The usefulness of these estimates in comparison with the ones provided by the GLOBOCAN (Ferlay *et al.*, 2013a) project for Portugal as a whole is that, in this work, estimates were calculated using data provided by a population-based cancer registry covering the geographical area under analysis, instead of using data from neighbouring regions/countries to perform such estimates. Furthermore, as there are marked differences within the country [namely, for some cancer types such as stomach (Lunet *et al.*, 2004) or thyroid (ROR-Centro, 2015), which are much more common in northern Portugal than in the rest of the country], this study provides further detailed information that is useful in the context of cancer control policies in this region.

In conclusion, this study contributes to a broader understanding of cancer burden in the north of Portugal, by providing incidence predictions up to 2020, which are useful in the context of cancer control policy making, and provide the basis for keeping population-based incidence estimates up to date.

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Conflicts of interest

There are no conflicts of interest.

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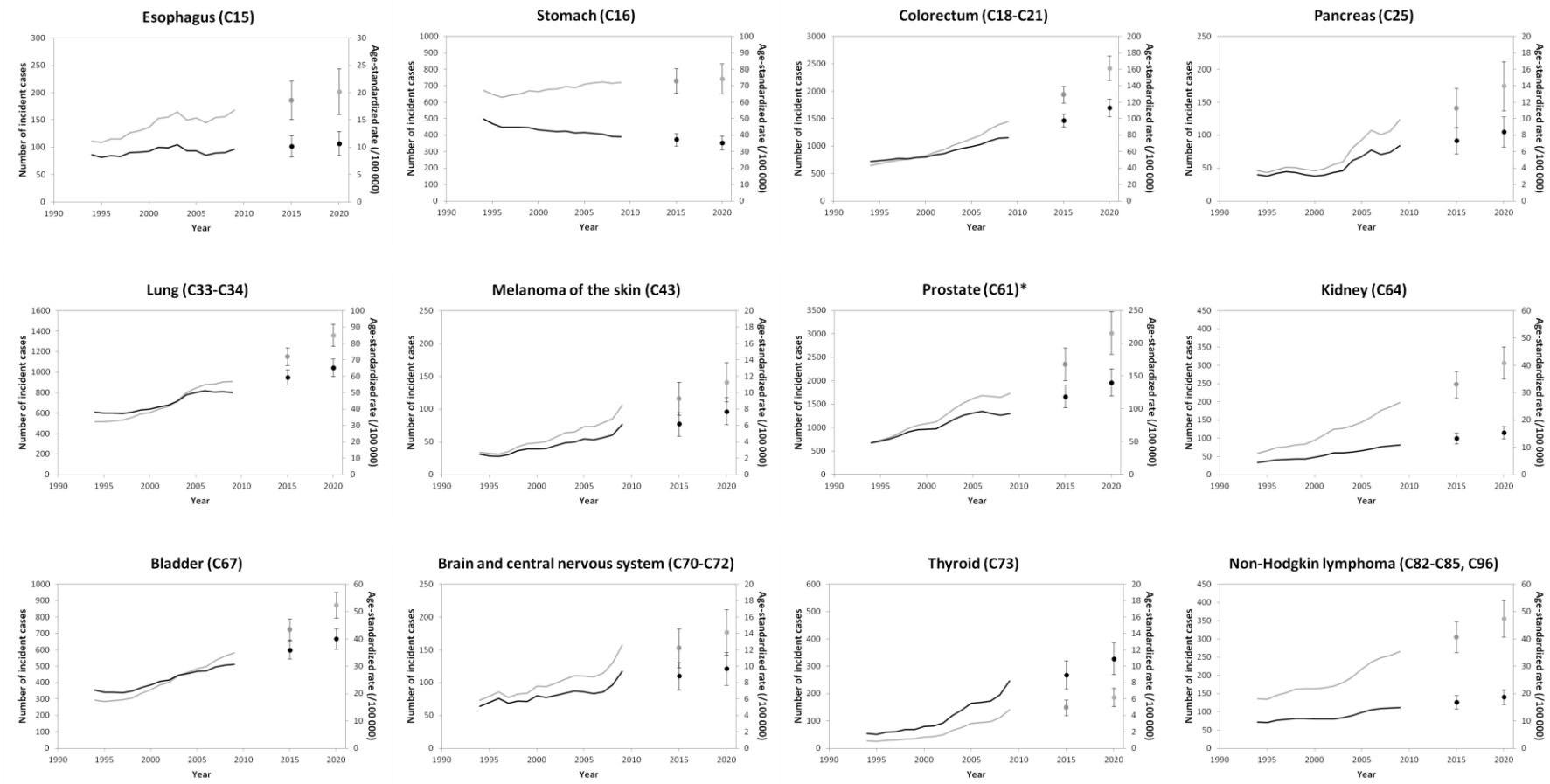
Supplementary Table 1: Number of cases (n), age-standardized incidence rates (ASIR) and corresponding 95% confidence intervals (95%CI), for 2015 and 2020, by cancer site and by sex.

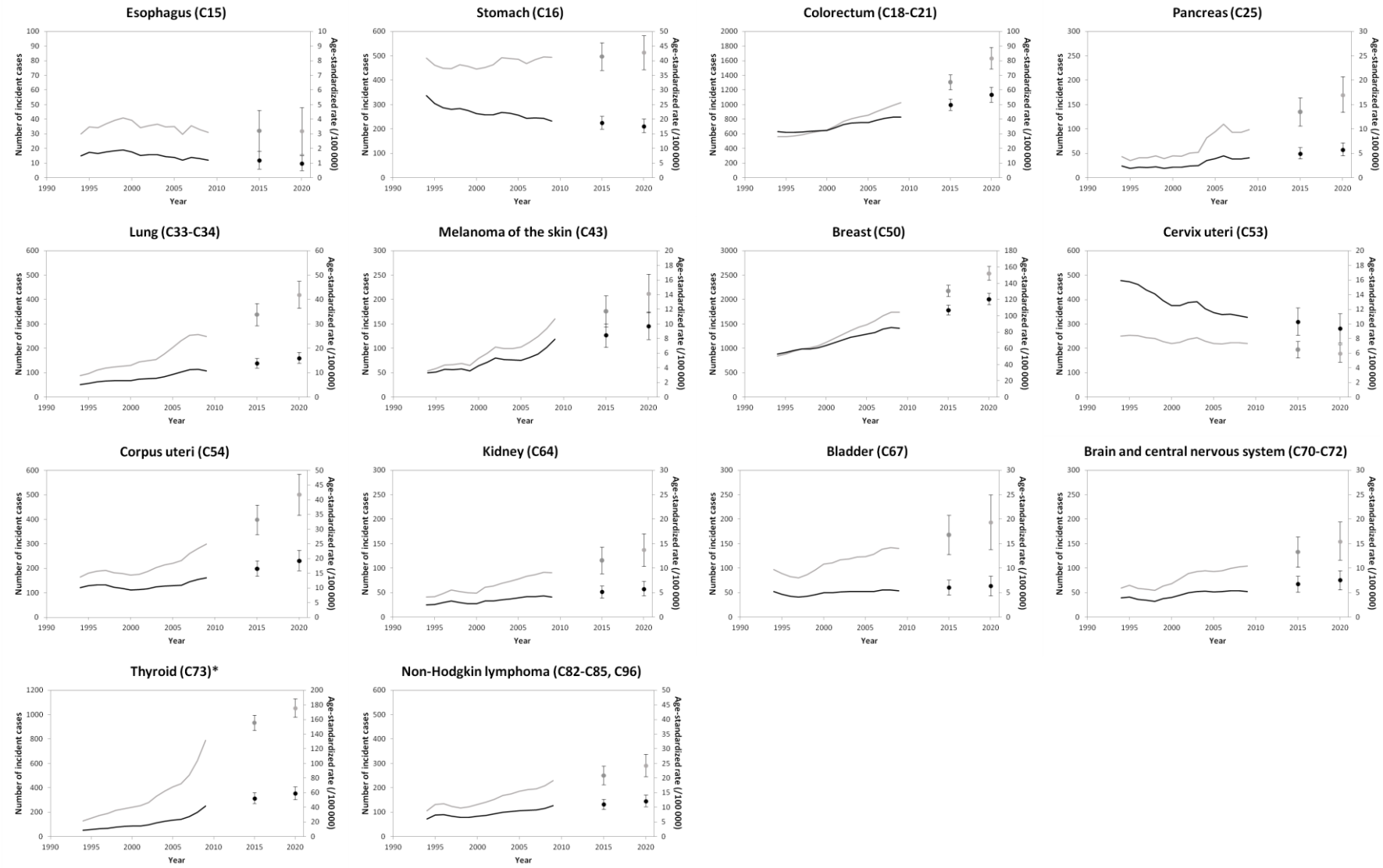
Cancer site (ICD-10)	Men - 2015		Men - 2020		Women - 2015		Women - 2020	
	n (95% CI)	ASIR (95% CI)	n (95% CI)	ASIR (95% CI)	n (95% CI)	ASIR (95% CI)	n (95% CI)	ASIR (95% CI)
All cancers (except skin non-melanoma)	9057 (8541 - 9573)	473.1 (446.0 - 500.2)	10236 (9379 - 11094)	500.8 (458.9 - 542.6)	8243 (7978 - 8507)	373.5 (361.0 - 385.9)	9820 (9463 - 10178)	422.4 (406.4 - 438.3)
Esophagus (C15)	186 (151 - 220)	10.2 (8.3 - 12.1)	202 (160 - 243)	10.7 (8.5 - 12.9)	32 (18 - 47)	1.2 (0.6 - 1.7)	32 (16 - 48)	1.0 (0.5 - 1.6)
Stomach (C16)	729 (655 - 803)	37.3 (33.5 - 41.0)	743 (653 - 833)	35.4 (31.2 - 39.7)	497 (441 - 554)	18.8 (16.6 - 21.0)	514 (446 - 584)	17.7 (15.3 - 20.0)
Colorectum (C18-C21)	1939 (1783 - 2094)	97.8 (89.8 - 105.7)	2421 (2194 - 2647)	113.1 (102.4 - 123.8)	1234 (1148 - 1319)	47.7 (44.2 - 51.2)	1464 (1359 - 1569)	52.0 (48.0 - 56.0)
Pancreas (C25)	141 (111 - 171)	7.3 (5.7 - 8.9)	175 (138 - 213)	8.4 (6.6 - 10.2)	135 (106 - 164)	5.0 (3.9 - 6.2)	170 (133 - 206)	5.8 (4.5 - 7.2)
Lung (C33-C34)	1151 (1063 - 1239)	59.4 (54.8 - 64.0)	1360 (1251 - 1469)	65.2 (59.9 - 70.5)	338 (293 - 384)	14.0 (12.0 - 16.0)	420 (364 - 476)	16.1 (13.9 - 18.4)
Melanoma of the skin (C43)	116 (91 - 141)	6.2 (4.7 - 7.6)	141 (111 - 171)	7.7 (6.0 - 9.3)	176 (144 - 208)	8.5 (6.8 - 10.0)	212 (172 - 251)	9.7 (7.9 - 11.6)
Female breast (C50)	NA	NA	NA	NA	2177 (2060 - 2294)	107.2 (101.3 - 113.2)	2541 (2398 - 2682)	120.6 (113.7 - 127.5)
Cervix uteri (C53)	NA	NA	NA	NA	195 (161 - 229)	10.3 (8.5 - 12.2)	179 (143 - 215)	9.4 (7.4 - 11.4)
Corpus uteri (C54)	NA	NA	NA	NA	398 (338 - 458)	16.6 (14.0 - 19.2)	501 (417 - 585)	19.3 (15.9 - 22.8)
Prostate (C61)	2351 (2009 - 2695)	119.1 (102.1 - 136.3)	3016 (2567 - 3471)	140.6 (120.1 - 161.5)	NA	NA	NA	NA
Kidney (C64)	248 (212 - 285)	13.3 (11.3 - 15.3)	307 (263 - 351)	15.4 (13.2 - 17.7)	116 (89 - 143)	5.2 (3.9 - 6.4)	138 (104 - 170)	5.8 (4.4 - 7.3)
Bladder (C67)	724 (659 - 789)	35.9 (32.7 - 39.2)	873 (794 - 953)	40.0 (36.3 - 43.7)	168 (128 - 208)	6.1 (4.5 - 7.6)	194 (138 - 250)	6.4 (4.4 - 8.4)
Brain and CNS (C70-C72)	153 (124 - 183)	8.8 (7.1 - 10.5)	177 (142 - 212)	9.7 (7.7 - 11.7)	133 (102 - 164)	6.8 (5.1 - 8.4)	155 (117 - 194)	7.6 (5.6 - 9.5)
Thyroid (C73)	149 (121 - 178)	8.9 (7.2 - 10.7)	186 (152 - 220)	10.9 (8.9 - 12.8)	934 (870 - 997)	52.6 (45.3 - 59.9)	1055 (980 - 1130)	59.3 (50.7 - 67.9)
Non-Hodgkin Lymphoma (C82-C85, C96)	305 (263 - 347)	16.9 (14.5 - 19.2)	356 (306 - 407)	18.7 (16.1 - 21.4)	250 (212 - 289)	11.1 (9.3 - 12.8)	292 (246 - 338)	12.2 (10.2 - 14.2)

NA: Not applicable; CNS: central nervous system



*we assumed that the increasing rate observed up to 2006 would become apparent again in future years, after the decline observed in the most recent years

Supplemental Figure 1: Trends in 3-year moving averages of the number of cases and age-standardized (all ages, direct method, European standard population) incidence rates in 1994-2009 (in grey and black, respectively) and predictions for 2015 and 2020, by cancer site, among men.



*we assumed that the increasing rate observed up to 2006 would hold in future years, instead of the steep increase observed onwards.

Supplemental Figure 2: Trends in 3-year moving averages of the number of cases and age-standardized (all ages, direct method, European standard population) incidence rates in 1994-2009 (in grey and black, respectively) and predictions for 2015 and 2020, by cancer site, among women.

Paper III

Castro C, Peleteiro B, Bento MJ, Lunet N.

TRENDS IN GASTRIC AND ESOPHAGEAL CANCERS INCIDENCE IN NORTHERN PORTUGAL (1994-2009), BY SUBSITE AND HISTOLOGY, AND PREDICTIONS FOR 2015.

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TRENDS IN GASTRIC AND ESOPHAGEAL CANCERS INCIDENCE IN NORTHERN PORTUGAL (1994-2009), BY SUBSITE AND HISTOLOGY, AND PREDICTIONS FOR 2015

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ABSTRACT

Introduction: Gastric (GC) and esophageal (EC) cancers share risk factors, and incidence trends reflect differences in etiology according to their subtypes. We aimed to describe GC (by topography) and EC (by histological type) incidence trends in Northern Portugal for 1994-2009, and estimate incidence in 2015. We further analyzed exposure to the main risk factors for these cancers in the region over the last decades.

Methods: GC and EC data were obtained from North Region Cancer Registry of Portugal (RORENO). Joinpoint regression was used to compute annual percent changes (APC) in incidence trends. Poisson regression yielded estimates for 2015. A literature review up to 2014 provided data on exposure to risk factors.

Results: GC rates decreased in 1994-2009 (men, APC=-1.3; women, APC=-1.6); GC unspecified subtype had the steepest decline, since the early 2000s (men, APC=-4.9; women, APC=-6.3). Incidence for 2015 will increase for EC in men (up to ≈190 cases) and stabilize in women (≈30) and for GC (≈730 men, ≈500 women). Increasing prevalences of tobacco smoking among women and overweight/obesity, fairly stable prevalences of alcohol, fruit and vegetable consumptions, and no trend for *Helicobacter pylori* infection were observed.

Conclusion: The declining incidence of GC unspecified subtype showed improvements in cancer registration, but precluded a sound assessment of trends by subtype. Variations in the prevalence of exposure to some risk factors were consistent with observed incidence trends, and future studies should aim to quantify their contribution to GC and EC burden in the region.

KEYWORDS

Esophageal neoplasms; Incidence; Stomach neoplasms; Trends.

INTRODUCTION

Gastric and esophageal cancers are among the ten most common worldwide, jointly accounting for 10% of the overall number of incident cases[1]. Both tumors present a low survival: in Europe, a recent study yielded 5-year relative survival rates of 25% and 12% for gastric and esophageal cancer, respectively[2].

Stomach cancer incidence and mortality have been decreasing for several decades, which is mainly attributable to the decrease in the frequency of *Helicobacter pylori* (*H. pylori*) infection, smoking, salt intake, and low consumption of fruits and vegetables[3, 4]. However, trends are not homogeneous across gastric cancer subtypes, as the decline has been greater for non-cardia gastric tumors, while for cardia tumors, in many settings, the pattern of variation resembles more closely the observed for esophageal cancer[3, 5].

Esophageal cancer is much less frequent than gastric cancer in more developed countries. There is a heterogeneous distribution of its main histological types, esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC), across countries, reflecting differences in the etiology of these subtypes. Overall, the incidence of esophageal cancer has been increasing in many of the most developed countries, mainly due to upward trends in EAC, possibly on account of higher prevalences of obesity and gastro-esophageal reflux[6]. The main risk factors for ESCC are smoking and alcohol consumption, and studies have shown their independent and synergistic effects[7]. *H. pylori* infection is negatively associated with EAC[8] and decreases in the prevalence of infection are expected to translate into a higher esophageal cancer morbidity[9]. Low fruit and vegetable intake increases the risk of both EAC and ESCC, and variations in their consumption are also expected to influence the trends in esophageal cancer incidence and mortality.

This study aimed to describe subtype-specific incidence trends in stomach (cardia and non-cardia) and esophageal cancers (squamous cell carcinoma (ESCC) and EAC) in Northern Portugal between 1994 and 2009, and to estimate the number of incident cases and age-standardized rates for 2015. It further analyzed the exposure to the main risk factors for these cancers in the region over the last decades.

METHODS

Incidence data on stomach and esophagus cancers for the period 1994-2009 were retrieved from the North Region Cancer Registry of Portugal (RORENO); this is a population-based cancer registry, set up in 1988, which covers approximately 3.2 million people who live in the five districts of Northern Portugal (Braga, Bragança, Porto, Viana do Castelo and Vila Real). For the same period, population figures based on official censuses were obtained from Statistics Portugal[10].

Sex-specific incidence rates were computed for each 5-year age group and calendar period, and age-standardized rates were calculated by the direct method, using the European standard population[11], for all ages and the age groups <65 and ≥65 years. Poisson regression analyses were performed using Joinpoint software[12], in order to identify significant changes in incidence trends (allowing for up to two joinpoints). For each of the segments obtained in the best model, the estimated annual percent change (APC) and corresponding confidence intervals (CI) were computed by fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable.

Stomach cancer incidence trends were analyzed overall and by sub-location according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3), *i.e.*, cardia (C16.0), non-cardia (C16.1-C16.6) and unspecified topography (C16.8-C16.9). Esophageal cancer incidence trends were analyzed overall and by histological type: ESCC (M8050/3-M8084/3), EAC (M8140/3-M8384/3), and other and unspecified esophageal cancers (all other morphology codes).

Population predictions up to 2015 were computed by RORENO, using a scenario of the evolution of resident population based on a constant fertility rate and on migration rates derived from available population figures from Statistics Portugal up to 2012. Predicted absolute numbers of cases of stomach and esophageal cancers for the year 2015, and the corresponding 95% prediction intervals[13, 14], were computed through linear (for increasing or stabilizing trends) or log-linear (for decreasing trends) Poisson regression analyses, by age group (0-34, 35-44, 45-54, 55-64, 65-74, 75-84 and ≥85 years). The last periods of time obtained in sex- and site-specific joinpoint models were used as a basis for the predictions. Age-standardized incidence rates were computed using the projected absolute number of cases and corresponding population estimates. The year 2015 was chosen as prediction limit to allow for international comparisons, using data from GLOBOCAN[1].

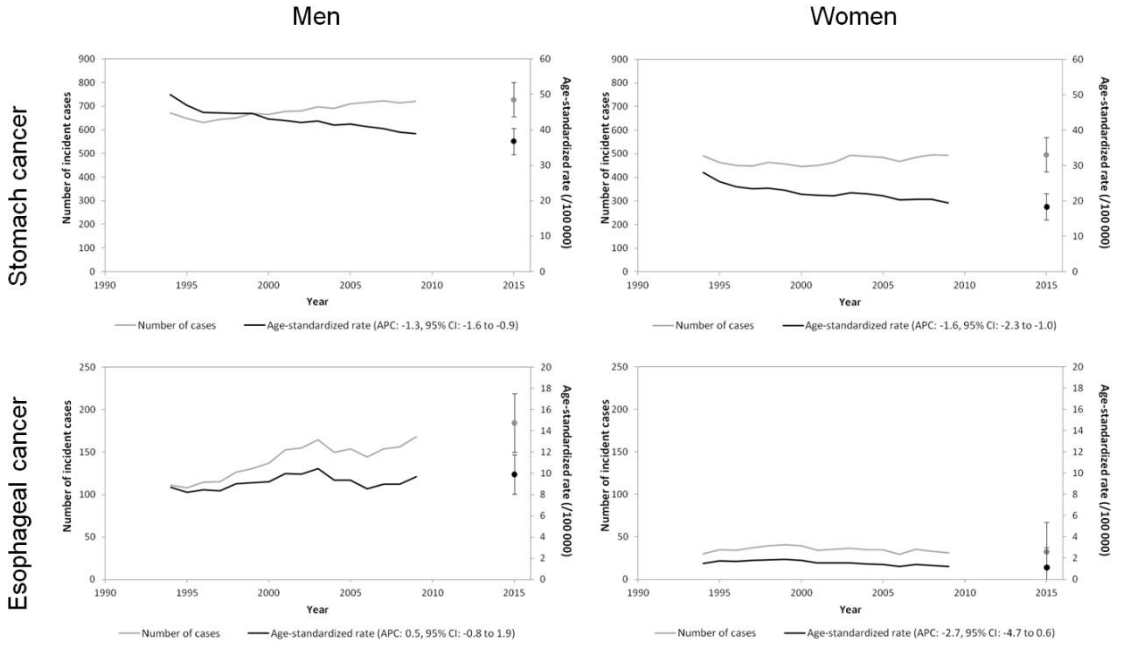
The variation in the prevalence of exposure to major determinants of gastric and/or esophageal cancers (tobacco smoking, alcohol drinking, overweight/obesity, *H. pylori* infection, and fruit and vegetable consumption) was evaluated by reviewing studies, published up to 2014, providing data from Northern Portugal. For tobacco smoking, overweight/obesity and *H. pylori* infection, previously published systematic reviews of Portuguese studies[15-17] were used as the primary source of published reports. For *H. pylori* infection, the systematic review was based on searches in PubMed and in the online database of the publications in Portuguese medical journals, from inception to July 2014. For smoking and overweight/obesity, PubMed was searched from inception up to 2011. Data obtained in these reviews were complemented by information from National Health Surveys. For alcohol drinking, and fruit and vegetable consumption, information was collected from National Health Surveys and from studies using the population-based cohorts EPIPorto (adults), EPITeen (adolescents) and Geração XXI (children) from Porto, the largest city in the region. Overall, sex- and age-group specific estimates were collected, whenever available. To describe the variation in exposure to the risk factors, only the overall-

and sex-specific estimates were used. For a graphical display of results, when two studies described the prevalence of exposure to the same risk factor in the same period of time, the estimate used was the one with the most similar selection criteria to the remaining studies on that risk factor.

RESULTS

In Northern Portugal, gastric cancer standardized rates significantly decreased since 1994, both among men (APC=-1.3, 95%CI: -1.6 to -0.9) and women (APC=-1.6, 95%CI: -2.3 to -1.0), while for the incidence of esophageal cancer, no significant variation was observed in the same period (Figure 1). The age groups <65 and ≥65 years presented similar trends, both for gastric (men: <65 years, APC=-0.6, 95%CI: -1.4 to 0.2, ≥65 years, APC=-0.3, 95%CI: -0.9 to 0.3; women: <65 years, APC=-1.3, 95%CI: -2.1 to -0.5, ≥65 years, APC=-0.2, 95%CI: -1.0 to 0.7), and esophageal (men: <65 years, APC=2.1, 95%CI: 0.2 to 3.9, ≥65 years, APC=0.8, 95%CI: -0.8 to 2.4; women: <65 years, APC=-1.5, 95%CI: -3.4 to 0.5, ≥65 years, APC=-1.5, 95%CI: -4.7 to 1.9) cancers.

The estimated number of cases in Northern Portugal for 2015 was 1224 (men, 728; women, 496) for gastric and 218 (men, 184; women, 34) for esophageal cancers. In relation to the estimated overall number of incident cancer cases in the region[18] these corresponded to 8.0% and 2.1% among men, respectively, and to 6.0% and 0.4% among women, respectively (Figure 1 and Table 1).



APC: annual percent change in 1994-2009; 95% CI: 95% confidence interval.
* figures depict 3-year moving averages

Figure 1: Sex-specific trends* in the absolute number of cases and age-standardized (all ages, direct method, European standard population) incidence rates for stomach and esophageal cancers in 1994-2009, and predictions to 2015.

Table 1: Absolute number of new cases (n) of gastric and esophageal cancers expected for 2015 and corresponding proportion in relation to the total number of cases, in Northern Portugal and selected countries (source: GLOBOCAN[1]), by sex.

Sex	Country/Region	All cancers*	Gastric cancer		Esophageal cancer	
		n	n	% of all cancers	n	% of all cancers
Men	RORENO	9057†	729	8.0	186	2.1
	Portugal	29397	1898	6.5	550	1.9
	Spain	135954	5147	3.8	1865	1.4
	Germany	286424	10845	3.8	5816	2.0
	Italy	200137	7915	4.0	1395	0.7
	Sweden	29128	524	1.8	356	1.2
	Ukraine	69649	6877	9.9	1647	2.4
	Australia	75377	1457	1.9	1127	1.5
	USA	903319	14408	1.6	14799	1.6
	Japan	441132	79350	18.0	17468	4.0
Women	RORENO	8243†	497	6.0	32	0.4
	Portugal	21241	1223	5.8	77	0.4
	Spain	91122	3100	3.4	353	0.4
	Germany	232229	6231	2.7	1485	0.6
	Italy	167768	5654	3.4	490	0.3
	Sweden	23486	327	1.4	126	0.5
	Ukraine	71980	4547	6.3	260	0.4
	Australia	56096	765	1.4	450	0.8
	USA	827542	8473	1.0	3744	0.5
	Japan	308370	36217	11.7	3333	1.1

*except non-melanoma skin cancer

†source: Castro *et al*.[18]

Figure 2 depicts the trends between 1994 and 2009 according to gastric cancer sub-location and esophageal cancer histological type. For gastric cancer, the steepest variation was a decline since the early 2000s in rates of tumors with unspecified location within the stomach, both among men (APC=-4.9, 95%CI: -7.6 to -2.0) and women (APC=-6.3, 95%CI: -10.6 to -1.7), along with increasing trends of a similar magnitude in non-cardia cancers in the same period (APC=5.2, 95%CI: 2.1 to 8.3 for men and APC=5.4, 95%CI: 3.0 to 7.9 for women). The incidence of cardia cancer decreased since 1994, though the variation was only statistically significant among women. In 2003-2007, gastric cancer with unspecified location accounted for more than two-thirds of all gastric cancer cases registered by RORENO, while the ratio non-cardia/cardia was 3.4 in men and 5.4 in women (Table 2).

For esophageal cancers, no significant variation was observed for any subtype among men, despite an upward trend for ESCC and a decline in EAC and unspecified/other tumors. Among women, there was a significant downward trend in ESCC (APC=-3.1) and non-significant increases for EAC and unspecified/other tumors (Figure 2). In 2003-2007, the overall proportion

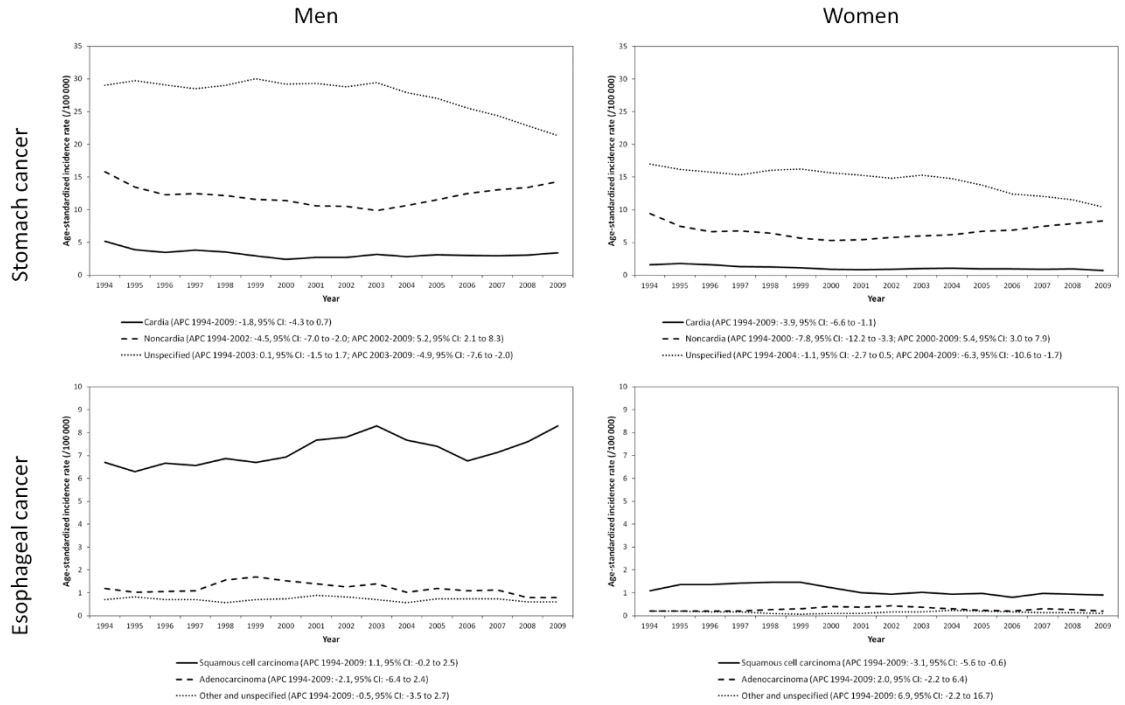


Figure 2: Number of cancer cases (n) diagnosed in 2003-2007 in Northern Portugal and selected geographical areas* (source: Cancer Incidence in Five Continents, volume X[50]) and corresponding proportion of cancer subtypes (%), by cancer site and by sex.

of esophageal cancers with other/unspecified histological type was less than 10%, and the ratio ESCC/EAC was 6.0 in men and 3.6 in women (Table 2).

Figure 3 depicts the variation in the prevalence of exposure to tobacco smoking, alcohol drinking, overweight/obesity, *H. pylori* infection, and fruit and vegetable consumption in Northern Portugal. Overall, sex- and age-group specific estimates are presented in Supplementary Table 1. Among adults, the prevalence of tobacco smoking[19-29] decreased for men, from 35% in 1987 to 25% in 2007, while for women it increased from 4% to 19%. The prevalence of alcohol drinking[22-25, 30-34] slightly increased for adult men, from 81% in 1987 to 86% in 2011, and decreased among adult women, from 58% to 53%. Among adults, the prevalence of overweight varied from 18% to 40% for men and from 16% to 33% for women; the prevalence of obesity varied from 8% to 15% for men and from 11% to 15% for women. Among children/adolescents aged 6-13 years, overweight increased from 21% to 23% for boys and from 19% to 22% for girls between 2003 and 2008, while obesity increased from 7% to 9% for boys and from 6% to 10% for girls in the same period[23-25, 35-37]. For *H. pylori* infection[38-44], seven studies were conducted in Northern Portugal, which targeted population at different age ranges, and no clear trends were observed among adults or children. The consumption of fruits and vegetables[23, 24, 32, 45-48] showed relatively stable trends, with the consumption of fruits being higher than that of vegetables, except among children, reflecting a high consumption of vegetable soup in this age group.

Table 2: Number of cancer cases (n) diagnosed in 2003-2007 in Northern Portugal and selected geographical areas* (source: Cancer Incidence in Five Continents, volume X[50]) and corresponding proportion of cancer subtypes (%), by cancer site and by sex.

Sex	Country/Region	Gastric cancer†					Esophageal cancer‡				
		n	% unspecified	% cardia	% non-cardia	ratio non-cardia/cardia	n	% unspecified	% ESCC	% EAC	ratio ESCC/EAC
Men	RORENO	3525	68.1	7.3	24.7	3.4	748	7.4	79.4	13.2	6.0
	Spain (13 registries)	5914	50.3	14.7	35.0	2.4	2373	11.6	62.2	26.2	2.4
	Germany (9 registries)	13411	40.4	21.9	37.7	1.7	6336	16.7	56.1	27.2	2.1
	Italy (33 registries)	16148	50.6	12.3	37.1	3.0	3247	18.6	57.1	24.3	2.3
	Ukraine (national)	39350	38.1	12.4	49.5	4.0	8078	36.5	52.9	10.6	5.0
	Sweden (national)	2909	71.8	28.2	0.0	-	1486	6.5	38.8	54.7	0.7
	Australia (national)	6165	42.9	34.1	23.1	0.7	4088	13.0	31.1	55.9	0.6
	USA (42 states)	56113	36.6	36.0	27.4	0.8	52617	11.8	26.0	62.2	0.4
	Japan (8 registries)	56165	39.8	6.5	53.7	8.2	11756	18.9	78.0	3.2	24.6
Women	RORENO	2390	67.8	5.0	27.2	5.4	168	13.1	67.9	19.0	3.6
	Spain (13 registries)	3424	52.5	6.9	40.6	5.9	375	16.5	60.0	23.5	2.6
	Germany (9 registries)	10202	45.8	10.6	43.5	4.1	1693	22.5	59.3	18.2	3.3
	Italy (33 registries)	11623	51.6	5.8	42.5	7.3	1093	28.6	57.0	14.4	4.0
	Ukraine (national)	26720	39.2	8.9	51.9	5.8	1256	51.2	31.6	17.2	1.8
	Sweden (national)	1839	86.0	14.0	0.0	-	535	7.1	59.3	33.6	1.8
	Australia (national)	3317	55.1	17.7	27.2	1.5	1913	17.3	58.3	24.4	2.4
	USA (42 states)	36044	46.8	16.5	36.7	2.2	15211	14.3	49.1	36.6	1.3
	Japan (8 registries)	27069	42.9	4.6	52.5	11.4	2209	26.3	70.1	3.6	19.6

*when data from more than one cancer registry were available in the same country, we added the number of incident cases from all registries
†includes ICD-O-3 codes C16.0 as cardia, C16.1-C16.4 as non-cardia and C16.5-C16.9 as unspecified location in the stomach
‡unspecified tumors include ICD-O-3 morphologies other than squamous cell carcinoma (ESCC) and adenocarcinoma (EAC)

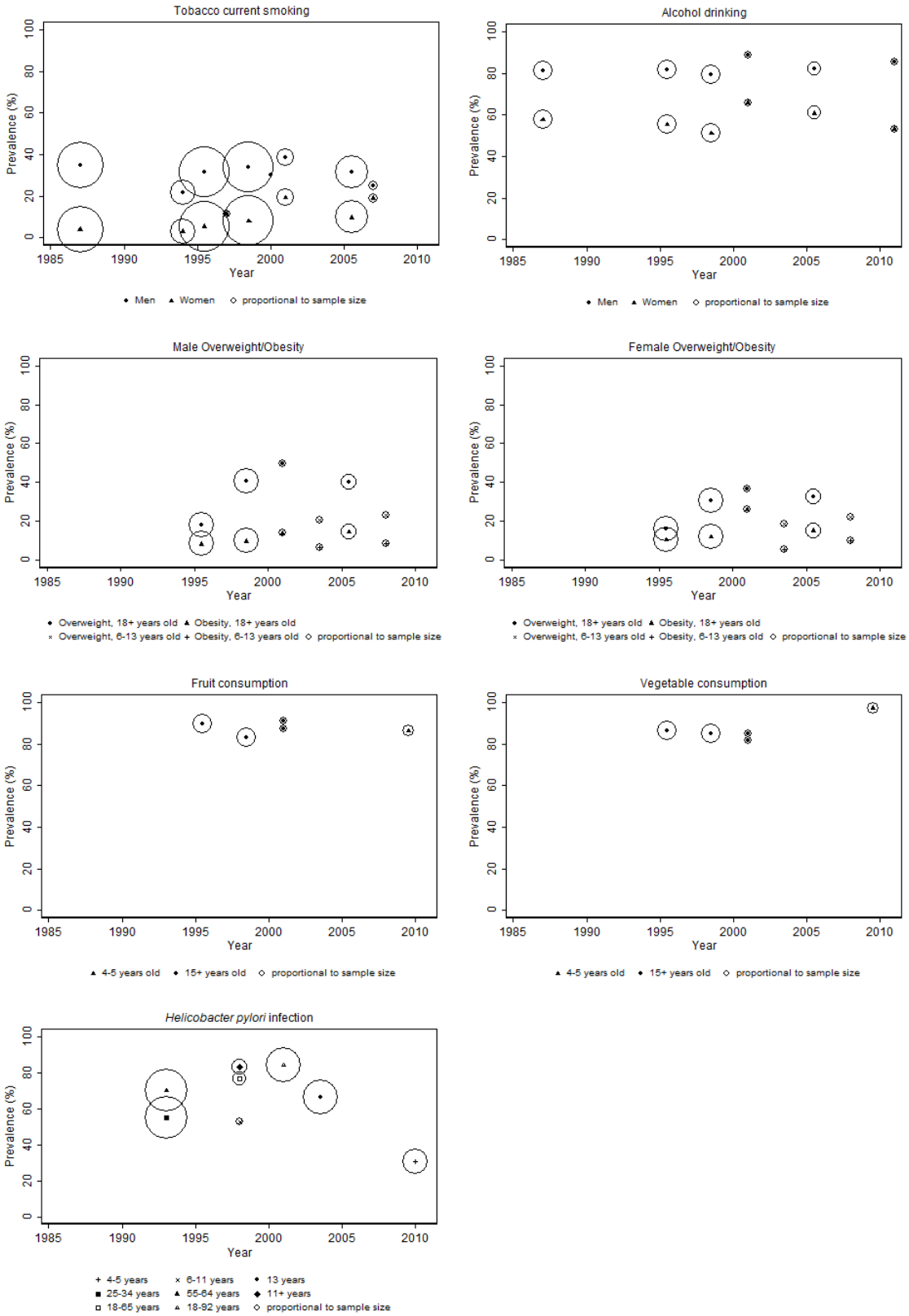


Figure 3: Variation in the exposure to major gastric and/or esophageal cancer determinants in Northern Portugal.

DISCUSSION

In Northern Portugal, the incidence of gastric cancer has been declining, but it remains the 4th most frequent cancer, whereas for esophageal cancer, there was no statistically significant variation, and it currently accounts for a much smaller proportion of all cancers registered, especially among women, ranking below 10th[49].

A wide variation between populations was observed, especially among men, regarding the proportion of gastric and esophageal cancers in the total number of expected cancers for 2015[1, 50]. Among the regions/countries considered in our study, male gastric cancer was estimated to account for between 1.6% (in the USA) and 18.0% (in Japan) of all cancers diagnosed in 2015, while male esophageal cancer represented between 0.7% (in Italy) and 4.0% (in Japan) of all cancers. For gastric cancer, the variability in the proportions found followed the patterns observed in cancer incidence, with countries with the highest incidence rates also presenting the highest proportions in relation to all cancers diagnosed; Northern Portugal had the third highest values, after Japan and Ukraine, and represented approximately double of the expected for Spain (8.0 vs. 3.8% for men and 6.0 vs. 3.4% for women). Portugal as a whole presented lower values, which was expected since gastric cancer is more frequent in the Northern region than in the rest of the country[51].

In relation to the proportion of cases of cardia and non-cardia subtypes, the differences observed are in accordance with a recent study showing that countries with high gastric cancer mortality rates present the lowest proportions of cardia cancers[3]. Regarding trends by subtype, the steep decline in the rates of tumors with unspecified location within the stomach is noteworthy. However, since unspecified gastric cancer still comprise the majority of stomach cancer cases in Northern Portugal, this precludes a sound interpretation of the trends in the rates of cardia and non-cardia cancers; the increasing rates observed for non-cardia cancers are unexpected, and most likely explained by a reduction in tumors with unspecified location mostly among the non-cardia cancers, which in Northern Portugal are much more frequent than those located in the cardia. The decreasing trends in rates of tumors with unspecified location within the stomach reflect improvements in cancer registration accuracy in RORENO, although there is still margin for improvement at this level[52].

For esophageal cancer, the proportion of unspecified tumors was among the lowest when compared with other European countries[5] and with the USA, Australia and Japan. The only significant change in trends regarding esophageal cancer subtypes in Northern Portugal was observed for ESCC among women, which was found declining. This pattern has also been observed in European countries such as France or Poland[5], although it is difficult to interpret in terms of changes in exposure to risk factors, on account of the much lower rates observed for women, in comparison with men. Among men, Joinpoint analyses were unable to detect significant changes in trends, although a peak and a minimum were observed for ESCC in 2003 and 2006, respectively. These variations may be due to random fluctuations, but overdispersion

in data could also be present. For both sexes, the majority of the esophageal cancers in Northern Portugal were ESCC, as observed in most European countries[5].

The prevalence of smoking in Northern Portugal steadily increased among women and decreased among men over the last decades, which is in accordance with the previously observed for Portugal as a whole[15]. The patterns of alcohol consumption found in the region seemed different from the ones previously described for the country, for which a long-term and marked decrease in overall alcohol consumption had been portrayed in international evaluations[53]. However, these comparisons are not straightforward: in international studies, data usually is related to availability, estimated from production, import, export and sales data in each country [54]; in our study, we described the prevalence of alcohol consumption, rather than dose, since such data were not available at a regional level. Our results suggest that, in Northern Portugal, alcohol drinking is an important contributor to ESCC risk (the trends in the prevalence of alcohol consumption and in ESCC incidence rates are both upwards among men and downwards among women); for EAC, tobacco was more important (the trends in the prevalence of tobacco consumption and in EAC incidence rates are both downwards among men and upwards among women), which was expected given that alcohol intake influences ESCC risk but it has no association with EAC[55, 56]. Further studies should be performed in the region to quantify the contribution of each risk factor to the observed cancer trends, also taking into account the lag times between exposures and outcomes.

The increasing prevalence of overweight and obesity previously described for Portugal was also found in the Northern Region[16], although the interpretation of these figures is limited by the fact that no data could be obtained for the region in the years preceding 1995. Since a lag of 10 years has been described for the association between excess body mass index and EAC[57], this increasing prevalence may contribute to an increase in EAC incidence in the next few years, which has not yet been observed in the area.

H. pylori infection is a risk factor for both gastric and esophageal cancers. Worldwide, the steady decline in gastric cancer incidence and mortality trends over the last five decades has been mainly attributed to an increase in socioeconomic status, namely through a reduction in *H. pylori* infection[3] and better nutrition and food preservation practices[4]. However, the prevalence of *H. pylori* infection in Northern Portugal was found persistently high, with no clear trend detected, showing that there is a margin for further reducing the burden of gastric cancer, by lowering the prevalence of infection[17].

Regarding nutrition, we were only able to evaluate the consumption of fruits and vegetables and alcohol intake, since information on the consumption of salt, and of smoked and pickled foods in the region is scarce, not allowing for a trend evaluation.

Although this study is based on data from a relatively small country, Portugal presents the highest gastric cancer mortality rates in Western Europe, along with some of the highest prevalences of *H. pylori* infection in the most recent years; within Portugal, the North Region

has the highest gastric cancer incidence and mortality rates. Nevertheless, we have recently described different patterns of variation in gastric cancer mortality[3], showing that Portugal, Japan, Chile or Ukraine, among others, share the same pattern, characterized by some of the highest rates in the world, and declines around 2.5% per year over the last three decades. For esophageal cancer, Portugal is also among a group of countries including, for example, Russia, France and Italy, which have ESCC as the predominant histological type and decreasing mortality rates[5]. Finally, our extensive review provides an easy access to data on the main risk factors for these cancers, which may be useful for understanding the observed trends and for international comparisons with this objective.

In conclusion, the declining incidence of cancers with unspecified subtypes suggest an improvement in cancer registration in Northern Portugal, but limit, to a certain extent, the interpretation of trends according to cancer subtypes, mainly regarding gastric tumors. Further studies should be performed in the region to quantify the individual and joint contribution of risk factors to the observed cancer trends, to yield more informed predicted estimates.

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The authors declare no conflict of interest.

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Supplementary Table 1: Exposure to the main determinants of esophageal and gastric cancers in Northern Portugal.

Reference	Year of data collection	Sample size	Age range (years)	Exposure	Exposure measurement	Results
INE, 1988	1987	6056 men, 6584 women	All ages	Tobacco	Prevalence of current consumption	Men ≥15 years: 34.9% 15-19 years: 15.5% 20-39 years: 48.9% 40-59 years: 37.0% ≥60 years: 23.8% <20 cig/day: 34.0% ≥21 cig/day: 58.8% Women ≥15 years: 4.1% 15-19 years: 3.2% 20-39 years: 10.0% 40-59 years: 1.8% ≥60 years: 0.4% <20 cig/day: 64.0% ≥21 cig/day: 30.8%
				Alcohol	Prevalence of consumption the week before the survey	Men All ages: 66.8% ≥15 years: 81.1% <15 years: 20.8% 15-19 years: 55.7% 20-39 years: 83.7% 40-59 years: 89.3% ≥60 years: 82.0% Wine: 63.6% Beer: 16.6% Brandy: 11.6% Women All ages: 53.7% ≥15 years: 57.8% <15 years: 18.2% 15-19 years: 37.9% 20-39 years: 60.7% 40-59 years: 61.8% ≥60 years: 59.1% Wine: 48.0% Beer: 3.1% Brandy: 0.9%
EUROGAST, 1993	1993	3194	25-34, 55-64	*H. pylori*	Prevalence of infection (ELISA)	Both sexes, 25-34 years: 55.0% Both sexes, 55-64 years: 70.0%
da Costa, 1997	1994	1825 men, 1704 women	Mean age: 36.4 (men), 32.1 (women)	Tobacco	Prevalence of current consumption	Men: 21.6% Women: 3.1%
INE, 1998	1995-1996	6909 men, 7603 women	All ages	Tobacco	Prevalence of current consumption	Men All ages: 30.4% ≥15 years: 31.7% 15-24 years: 27.0% 25-34 years: 51.8% 35-44 years: 47.1% 45-54 years: 36.3% 55-64 years: 24.1% 64-74 years: 17.7% ≥75 years: 8.7% <20 cig/day: 28.7% ≥21 cig/day: 70.7% Women All ages: 5.0% ≥15 years: 5.4%

			15-24 years: 6.7% 25-34 years: 13.2% 35-44 years: 8.7% 45-54 years: 3.4% 55-64 years: 0.6% 64-74 years:0.6% ≥75 years: 0.0% <20 cig/day: 61.9% ≥21 cig/day: 37.0%
	Alcohol	Prevalence of consumption the year before the survey	Men All ages: 66.9% ≥15 years: 81.8% <15 years: 6.0% 15-17 years: 33.6% 18-24 years: 67.0% 25-34 years: 87.7% 35-44 years: 92.2% 45-54 years: 94.0% 55-64 years: 88.5% 65-74 years: 84.7% ≥75 years: 76.6% Wine: 62.1% Beer: 47.2% Women All ages: 46.9% ≥15 years: 55.4% <15 years: 6.0% 15-17 years: 20.8% 18-24 years: 38.8% 25-34 years: 59.9% 35-44 years: 67.0% 45-54 years: 66.0% 55-64 years: 61.0% 65-74 years: 56.4% ≥75 years: 49.3% Wine: 44.2% Beer: 13.6%
	Fruits	Prevalence of consumption the day before the survey	Both sexes All ages: 89.9% ≥15 years: 89.4% 0-4 years: 86.6% 5-14 years: 94.0% 15-17 years: 94.7% 18-24 years: 93.9% 25-34 years: 91.1% 35-44 years: 89.1% 45-54 years: 88.0% 55-64 years: 87.4% 65-74 years: 86.2% ≥75 years: 85.3%
	Vegetables	Prevalence of consumption the day before the survey	Both sexes All ages: 85.5% ≥15 years: 86.5% 0-4 years: 71.6% 5-14 years: 84.6% 15-17 years: 85.5% 18-24 years: 86.2% 25-34 years: 86.2% 35-44 years: 86.8% 45-54 years: 87.6% 55-64 years: 87.8% 65-74 years: 85.9% ≥75 years: 83.5%
	Obesity (BMI ≥ 30)	Prevalence	Men ≥18 years: 8.4% 18-24 years: 1.0%

						25-34 years: 5.1% 35-44 years: 8.0% 45-54 years: 12.0% 55-64 years: 14.0% 65-74 years: 12.1% ≥75 years: 9.6% Women ≥18 years: 10.5% 18-24 years: 1.9% 25-34 years: 4.6% 35-44 years: 10.1% 45-54 years: 15.6% 55-64 years: 15.5% 65-74 years: 16.9% ≥75 years: 8.3%
				Overweight (27 ≤ BMI < 30)	Prevalence	Men ≥18 years: 18.2% 18-24 years: 7.4% 25-34 years: 16.2% 35-44 years: 19.3% 45-54 years: 24.4% 55-64 years: 23.1% 65-74 years: 19.9% ≥75 years: 18.9% Women ≥18 years: 16.3% 18-24 years: 3.8% 25-34 years: 10.5% 35-44 years: 16.1% 45-54 years: 23.3% 55-64 years: 15.5% 65-74 years: 16.9% ≥75 years: 8.3%
Marques-Vidal, 2005	1995-1996	5553 men, 6296 women	≥15	Alcohol	Prevalence of consumption the week before the survey	Men Drinker: 73.1% Wine: 95.1% Beer: 72.3% Whiskey: 34.0% Port wine: 41.8% Women Drinker: 22.6% Wine: 92.0% Beer: 51.2% Whiskey: 27.7 % Port wine: 47.3 %
	1998-1999	5802 men, 6546 women	≥15	Alcohol	Prevalence of consumption the week before the survey	Men Drinker: 69.1% Wine: 93.4% Beer: 74.3% Whiskey: 35.5% Port wine: 35.9% Women Drinker: 22.5% Wine: 92.5% Beer: 48.4% Whiskey: 24.3% Port wine: 41.0%
Sallmen, 2008	1997	406 women	15-39	Tobacco	Prevalence of current consumption	Women, 15-39 years: 11.6%
Amaral, 1998	1998	211 men, 135 women	18-65	*H. pylori*	Prevalence of infection (ELISA)	Both sexes 18-65 years: 76.6% 18-25 years: 58.9%

						26-40 years: 74.5% 41-65 years: 87.6%
Pinho, 1998	1998	299 men, 162 women	≥11	*H. pylori*	Prevalence of infection (ELISA)	≥11 years: 82.9% 11-20 years: 58% 21-30 years: 71% 31-40 years: 91% 41-50 years: 90% ≥51+ years: 91%
Silva, 1999	1998	47 boys, 57 girls	6-11	*H. pylori*	Prevalence of infection (UBT)	Both sexes 6-11 years: 52.9% 6-8 years: 45.9% 9-11 years: 56.3% Boys, 6-11 years: 57.4% Girls, 6-11 years: 49.1%
INSA, 2001	1998-1999	5802 men, 6546 women	All ages	Tobacco	Prevalence of current consumption	Men ≥15 years: 34.1% 15-24 years: 27.7% 25-34 years: 49.4% 35-44 years: 47.7% 45-54 years: 32.5% 55-64 years: 23.3% 64-74 years: 16.9% ≥75 years: 9.0% <20 cig/day: 71.7% ≥21 cig/day: 25.9% Women ≥15 years: 8.0% 15-24 years: 10.3% 25-34 years: 16.2% 35-44 years: 11.1% 45-54 years: 5.1% 55-64 years: 1.7% 64-74 years: 0.5% ≥75 years: 0.7% <20 cig/day: 91.6% ≥21 cig/day: 6.3%
				Alcohol	Prevalence of consumption the year before the survey	Men ≥15 years: 79.2% <15 years: 1.6% 15-24 years: 47.9% 25-34 years: 85.2% 35-44 years: 91.3% 45-54 years: 90.6% 55-64 years: 88.3% 65-74 years: 82.6% ≥75 years: 75.3% Wine: 89.9% Beer: 74.9% Brandy: 29.7% Liquour: 35.3% Whiskey. Gin. Vodka: 35.0% Women ≥15 years: 51.2% <15 years: 1.1% 15-24 years: 23.3% 25-34 years: 52.9% 35-44 years: 67.4% 45-54 years: 60.8% 55-64 years: 57.2% 65-74 years: 52.8% ≥75 years: 46.0% Wine: 92.6% Beer: 28.3% Brandy: 2.6% Liquour: 26.3%

						Whiskey. Gin. Vodka: 8.7%
				Fruits	Prevalence of consumption the day before the survey	Both sexes All ages: 83.7% ≥15 years: 83.0% 0-4 years: 82.4% 5-14 years: 88.5% 15-24 years: 85.3% 25-64 years: 83.3% ≥65 years: 79.7%
				Vegetables	Prevalence of consumption the day before the survey	Both sexes All ages: 84.1% ≥15 years: 84.9% 0-4 years: 75.3% 5-14 years: 80.9% 15-24 years: 80.8% 25-64 years: 85.4% ≥65 years: 87.2%
				Overweight (25 ≤ BMI < 30)	Prevalence	Men ≥18 years: 40.6% 18-24 years: 22.2% 25-34 years: 36.8% 35-44 years: 45.6% 45-54 years: 47.0% 55-64 years: 48.0% 65-74 years: 47.7% ≥75 years: 42.2% Women ≥18 years: 30.7% 18-24 years: 11.3% 25-34 years: 23.5% 35-44 years: 34.5% 45-54 years: 38.2% 55-64 years: 42.0% 65-74 years: 37.7% ≥75 years: 31.0%
				Obesity (BMI ≥ 30)	Prevalence	Men ≥18 years: 9.9% 18-24 years: 1.8% 25-34 years: 6.6% 35-44 years: 10.3% 45-54 years: 15.3% 55-64 years: 15.3% 65-74 years: 14.3% ≥75 years: 9.8% Women ≥18 years: 12.1% 18-24 years: 2.3% 25-34 years: 6.2% 35-44 years: 11.3% 45-54 years: 19.2% 55-64 years: 18.7% 65-74 years: 17.6% ≥75 years: 13.3%
Correia, 2001	2000	40 men	33-73	Tobacco	Prevalence of current consumption	Men, 33-73 years: 30%
Bastos, 2013a	1999-2003	2067	18-92	*H. pylori*	Prevalence of infection (ELISA)	Both sexes 18-92 years: 84.2% 18-40 years: 75.3% 41-60 years: 89.0% 61-92 years: 89.5% Men, 18-92 years: 85.0% Women, 18-92 years: 83.7%

Lopes, 2006	1999-2003	921 men, 1477 women	18-92	Vegetables (not including soup)	Prevalence of daily consumption	Men ≥ 18 years: 81.5% 18-39 years: 82.1% 40-49 years: 85.0% 50-64 years: 80.4% ≥ 65 years: 79.7% Women ≥ 18 years: 84.8% 18-39 years:83.7% 40-49 years: 90.0% 50-64 years: 86.3% ≥ 65 years: 78.5%
				Fruits	Prevalence of daily consumption	Men ≥ 18 years: 87.4% 18-39 years: 83.8% 40-49 years: 86.5% 50-64 years: 89.5% ≥ 65 years: 88.2% Women ≥ 18 years: 91.0% 18-39 years: 85.3% 40-49 years: 91.8% 50-64 years: 93.4% ≥ 65 years: 91.7%
				Alcohol	Prevalence of daily consumption	Men ≥ 18 years: 68.8% 18-39 years: 40.2% 40-49 years: 75.5% 50-64 years: 78.4% ≥ 65 years: 72.8% Women ≥ 18 years: 25.3% 18-39 years: 9.7% 40-49 years: 27.6% 50-64 years: 32.0% ≥ 65 years: 27.1%
Santos, 2003	1999-2003	563 men, 873 women	18-92	Overweight (25 ≤ BMI < 30)	Prevalence	Men: 49.9% Women: 36.5%
				Obesity (BMI ≥ 30)	Prevalence	Men: 13.9% Women: 26.1%
Santos, 2004	1999-2003	629 men, 1015 women	18-92	Tobacco	Prevalence of current consumption	Men 18-24 years: 44.0% 25-34 years: 61.5% 35-44 years: 49.7% 45-54 years: 38.0% 55-64 years: 23.8% 64-74 years: 17.1% 75-93 years: 11.1% Women 18-24 years: 40.7% 25-34 years: 36.2% 35-44 years: 31.4% 45-54 years: 15.7% 55-64 years: 5.8% 64-74 years: 0.8% 75-93 years: 1.3%
Santos, 2007	1999-2003	832 men, 1332 women	18-92	Alcohol	Prevalence of consumption	Men Current/ocasional drinker: 88.8% Former drinker: 6.4%

						Never drinker: 4.8% Women Current/ocasional drinker: 65.8% Former drinker: 8.3% Never drinker: 25.9%
Clemente, 2004	2003	154 men, 226 women	18-30	Tobacco	Prevalence of daily consumption	Men: 10.4% Women: 16.4%
Bastos, 2013b	2003-2004	2204	13	*H. pylori*	Prevalence of infection (ELISA)	Both sexes: 66.2% Boys: 68.4% Girls: 63.6%
Fraga, 2011	2003-2004	946 boys, 1029 girls	13	Alcohol	Experimenter (ever experimented with alcohol), drinker (consumption at least once per month)	Boys Drinker: 6.6% Experimenter: 44.9% Girls Drinker: 4.7% Experimenter: 50.0%
Ramos, 2004	2003-2004	1135	13	Fruits	Daily mean consumption	Boys: 273g/day Girls: 303g/day
				Vegetables	Daily mean consumption	Boys: 147g/day Girls: 153g/day
Ramos, 2007	2003-2004	1045 boys, 1116 girls	3	Overweight	Prevalence, calculated using the International Obesity Taskforce Recommendations	Boys: 20.8% Girls: 18.8%
				Obesity	Prevalence, calculated using the International Obesity Taskforce Recommendations	Boys: 6.6% Girls: 5.7%
INE, 2008	2005-2006	3000 households	All ages	Fruits	Household expenses, in euros	213€ (1.3% of the expenses)
				Vegetables	Household expenses, in euros	241€ (1.4% of the expenses)
INSA, 2007	2005-2006	6084	All ages	Tobacco	Prevalence of current consumption	Men ≥15 years: 31.4% 15-24 years: 33.1% 25-34 years: 37.7% 35-44 years: 47.3% 45-54 years: 32.6% 55-64 years: 16.6% 64-74 years: 13.6% ≥75 years: 8.8% <20 cig/day: 75.4% ≥21 cig/day: 22.7% Women 15-74 years: 9.8% 15-24 years: 11.4% 25-34 years: 12.8% 35-44 years: 17.4% 45-54 years: 7.1% 55-64 years: 2.9% 64-74 years: 1.5% <20 cig/day: 92.8% ≥21 cig/day: 5.0%

	Alcohol	Prevalence of consumption the year before the survey	Men ≥15 years: 81.9% <15 years: 4.0% 15-24 years: 54.0% 25-34 years: 85.4% 35-44 years: 86.0% 45-54 years: 91.4% 55-64 years: 90.9% 65-74 years: 91.0% ≥75 years: 77.9% Wine: 91.1% Beer: 78.9% Brandy: 32.2% Liquour: 46.8% Whiskey. Gin. Vodka: 38.7% Women ≥15 years: 60.9% <15 years: 1.3% 15-24 years: 36.8% 25-34 years: 56.4% 35-44 years: 70.6% 45-54 years: 72.3% 55-64 years: 69.8% 65-74 years: 61.0% ≥75 years: 58.0% Wine: 89.8% Beer: 35.3% Brandy: 4.8% Liquour: 38.0% Whiskey. Gin. Vodka: 10.9%
	Overweight (25 ≤ BMI < 30)	Prevalence	Men ≥18 years: 40.0% 18-24 years: 18.0% 25-34 years: 39.2% 35-44 years: 41.0% 45-54 years: 48.7% 55-64 years: 47.8% 65-74 years: 42.9% ≥75 years: 42.3% Women ≥18 years: 32.8% 18-24 years: 15.1% 25-34 years: 21.6% 35-44 years: 35.5% 45-54 years: 36.7% 55-64 years: 43.9% 65-74 years: 43.6% ≥75 years: 34.9%
	Obesity (BMI ≥ 30)	Prevalence	Men ≥18 years: 14.6% 18-24 years: 5.0% 25-34 years: 7.1% 35-44 years: 14.1% 45-54 years: 21.2% 55-64 years: 21.2% 65-74 years: 23.5% ≥75 years: 15.7% Women ≥18 years: 15.2% 18-24 years: 5.0% 25-34 years: 9.5% 35-44 years: 11.5% 45-54 years: 22.6% 55-64 years: 24.7% 65-74 years: 20.0% ≥75 years: 14.4%

Lobão, 2010	2007	165 men, 337 women	18-84	Tobacco	Prevalence of current consumption	Men: 25% Women: 19%
Saleiro, 2008	2007	173 men, 165 women	17-41	Tobacco	Prevalence of current consumption	Men: 31.8% Women: 10.9%
Vasques, 2012	2008	907 boys, 879 girls	6-13	Overweight	Prevalence, calculated using the International Obesity Taskforce Recommendations	Boys: 23.2% Girls: 22.1%
				Obesity	Prevalence, calculated using the International Obesity Taskforce Recommendations	Boys: 8.7% Girls: 10.0%
Lopes, 2014	2009-2010	2942 boys, 2869 girls	4-5	Vegetables	Prevalence of daily consumption	Both sexes: 97.3%
					Daily mean consumption	Boys: 101.8 g/day Girls: 99.9 g/day
				Fruits	Prevalence of daily consumption	Both sexes: 86.2%
					Daily mean consumption	Boys: 168.7 g/day Girls: 163.8 g/day
Lunet, 2014	2009-2011	1047	4-5	*H. pylori*	Prevalence of infection (ELISA)	Both sexes: 30.6% Boys: 29.9% Girls: 31.4%
INE, 2012	2010-2011	3570 households	All ages	Fruits	Household expenses, in euros	219€ (1.1% of the expenses)
				Vegetables	Household expenses, in euros	244€ (1.2% of the expenses)
Dias, 2011	2011	925 men, 1489 women	18-92	Alcohol	Prevalence of current consumption	Men: 85.5% Women: 53.3%

BMI: Body mass index; *H. pylori*: *Helicobacter pylori*; ELISA: Enzyme-linked immunosorbent assay; UBT: Urea breath test.

Paper IV

Castro C, Peleteiro B, Lunet N.

MODIFIABLE FACTORS AND ESOPHAGEAL CANCER: A SYSTEMATIC REVIEW OF PUBLISHED META-ANALYSES.

(submitted)

MODIFIABLE FACTORS AND ESOPHAGEAL CANCER: A SYSTEMATIC REVIEW OF PUBLISHED META-ANALYSES

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ABSTRACT

Background: There are marked differences in the etiology of the major histological types of esophageal cancer (EC) – squamous cell carcinomas (ESCC) and adenocarcinomas (EAC). This study aimed to summarize the current scientific knowledge on modifiable risk factors for EC, by histological type.

Methods: A systematic review of meta-analyses referenced in PubMed and ISI Web of Knowledge until September 2015 was performed.

Results: We identified 95 meta-analyses on risk factors for ESCC (n=47), EAC (n=46) or EC (n=51). ESCC risk significantly increased with alcohol and maté drinking, smoking and red and processed meat consumption, while it was negatively associated with body mass index and consumption of fruit, vegetable, white meat, folate and some carotenoids. Cessation of drinking and smoking significantly reduced ESCC risk. For EAC, an increased risk was reported for smoking, body mass index, gastroesophageal reflux and red and processed meat consumption, while risk decreased with *Helicobacter pylori* infection, low/moderate alcohol drinking, physical activity and consumption of fruit, vegetables, folate, fiber, beta-carotene and vitamin C.

Conclusions: Differences in results between meta-analyses and mechanisms underlying some of the associations found are discussed. This work reinforces the importance of a separate assessment of EC subtypes to allow for a proper evaluation of incidence trends and planning of prevention/control interventions.

KEYWORDS

Adenocarcinoma; Carcinoma, Squamous Cell; Esophageal Neoplasms; Review; Risk factors.

INTRODUCTION

There are marked differences between the tumors of the major histological types of esophageal cancer (EC) regarding incidence and mortality trends, which reflect the specificities of each subtype regarding its determinants[1].

Esophageal squamous cell carcinoma (ESCC) comprises most cases of esophageal cancer[2], although its incidence has been steadily decreasing or stabilizing in Western countries[3]. The main risk factors of ESCC occurrence are tobacco smoking and alcohol consumption and many studies have shown both the independent and synergistic effects of these determinants[4].

Esophageal adenocarcinoma (EAC) incidence rates have been steadily increasing in several Western countries[3], although there are differences, either between countries[1] and between regions within the same country[5]. The upward trends are in part due to the increased prevalence of recognized risk factors such as gastroesophageal reflux disease (GERD) and obesity[6], but they may also be explained by variation in other modifiable exposures, such as smoking, diet and *Helicobacter pylori* (HP) infection[6-9].

A large body of research has been devoted to the study of the determinants of esophageal cancer, as summarized in several meta-analyses. This study aims to summarize the state of the art on the etiology of EC, by systematically reviewing published meta-analyses on the main modifiable factors associated with the occurrence of esophageal cancer, by histological type.

METHODS

PubMed and ISI Web of Knowledge were searched up to September 2015 to identify published meta-analyses addressing the association between the main modifiable exposures and esophageal cancer. The titles and abstracts of the retrieved articles were read and full texts were obtained for the studies considered potentially relevant. In addition, references cited in the identified articles were manually searched.

Studies were included if a meta-analysis based on published results or an individual participant data meta-analysis was performed to quantify the association between modifiable exposures and EC, ESCC or EAC. Only full-length papers published in English, Portuguese, Spanish, French, Italian or Polish were included. Studies focusing on the impact of the cessation of modifiable exposures on the risk of EC, EAC or ESCC were also kept in our review. Studies were excluded if: (1) EC, ESCC or EAC was not reported as an outcome of interest; (2) determinants other than alcohol drinking, smoking and smokeless tobacco, HP infection, GERD, Barrett's Esophagus, obesity/BMI, physical activity or diet were evaluated; (3) no summary estimate was provided in the form of an odds ratio (OR), relative risk (RR) or hazard ratio (HR), along with the correspondent 95% confidence interval (CI); (4) results provided constituted duplicate information from previous studies (i.e., reviews mentioning as summary estimate a result from a meta-analysis already included in our review).

Since EC is a relatively rare and a highly lethal disease, we ignored the distinction between RR, OR and HR, reporting RR henceforth as the effect estimate. For each study, the following information was extracted: first author's name, publication year, number of studies included in the meta-analysis and corresponding study design when available, EC histological type evaluated, risk factor assessed, categories of exposure compared, the RR and corresponding 95% CI. Stratified results by sex, study type and geographical area and dose-response RRs were collected, whenever available. If both fixed and random effects estimates were provided, the latter were used as they allow for some heterogeneity between studies.

All studies were assessed independently by two researchers (CC and BP) to determine their eligibility and for data extraction; disagreements were discussed and resolved by consensus or involving a third researcher (NL).

Each meta-analysis obtained from a systematic review was attributed a quality score, ranging from 0 to 11, based on the AMSTAR tool[10]. Results obtained were summarized using a harvest plot, for the most commonly evaluated determinants. Forest plots describing the overall and sex-specific RRs on the main determinants of EAC and ESCC were obtained using Stata Statistical Software, version 11.0[11].

RESULTS

We identified 95 publications reporting results from meta-analyses on the association between the aforementioned risk factors and the occurrence of ESCC (n=47), EAC (n=46) or EC (n=51). The systematic review flow-chart is presented as Supplementary Figure 1. Information extracted for each study is accessible in Supplementary Table 1, and quality assessment is presented in Figure 1 and Supplementary Table 2. The minimum and maximum quality scores found were of 3 and 10, respectively, and 47 meta-analyses had a score of 7 or higher. The main findings for each determinant of EC are presented below.

Alcohol drinking

Twenty five studies evaluated the association between alcohol drinking and EC, 11 of which did not include histology-specific RRs[12-22].

Eight studies reported a significant dose-response effect of alcohol drinking on EC, both in the overall[12, 13, 15, 16, 18, 23] and subgroup analyses by sex[12], geographical area (Mediterranean and Non-Mediterranean)[14], study design (case-control and cohort studies)[22] and type of drink

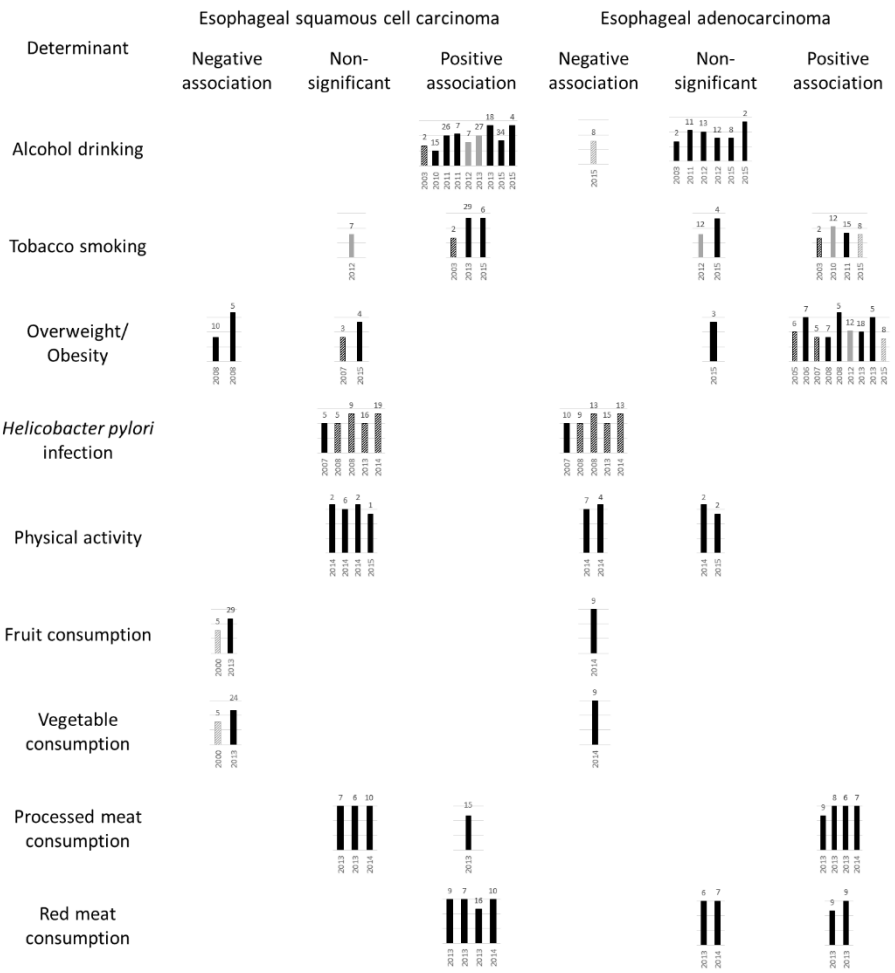

Figure 1: Harvest plot of the overall association between the main determinants of esophageal cancer and its occurrence, by subtype, when comparing the highest with the lowest levels of exposure or dose-response effects. Each bar corresponds to a meta-analysis (based on systematic reviews in black, otherwise in grey) and depicts its quality score; labels correspond to the number of studies included in the estimate provided in each meta-analysis; a diagonal pattern indicates that the estimate was obtained from case-control studies only. Meta-analyses are ordered according to year of publication (x-axis).

(wine[13] and beer[22]). Overall, an increment of 100g/week of alcohol consumption was found to increase EC risk by 15% (RR=1.15, 95%CI: 1.08, 1.22)[23].

The association between ESCC and alcohol consumption was addressed in 11 studies (Figure 2A)[23-33]. Sex-specific estimates showed a non-significantly higher ESCC risk among men than women: RRs were of 3.7 and 2.1, respectively, when comparing ever with never drinkers[26] and of 1.46 and 1.28 when comparing light drinkers with never drinkers[24]. Age at starting drinking and the number of drinking years did not relevantly change ESCC risk[26]. An increment of 100 g/week of alcohol consumption was found increasing ESCC risk by 20%[23]. A dose-response effect was also reported in meta-analyses evaluating alcohol consumption as the number of drinks per day[29, 31], drink-years[31] and grams of pure ethanol consumed per day or per week[24-26, 30, 33]. Among men, RRs ranged between 1.39 (95%CI: 1.11, 1.74) for 1-12.5 g/day and 4.69 (95%CI: 3.49, 6.31) for over 50 g/day, while among women corresponding values were of 1.14

(95%CI: 0.87, 1.49) and 8.32 (95%CI: 2.95, 23.45), when compared with non-drinkers[25]. No significant differences were found in ESCC risk between case-control and cohort studies[24, 25], nor between different geographical areas (Asia/Non-Asia[30], Europe/Asia[32] and Europe/Asia/North America[24, 25]).

Six meta-analyses reported on alcohol drinking and EAC (Figure 2B)[23, 28, 29, 31, 34, 35]. Two compared ever with never drinkers: while Drahos *et al.*[34] reported a significantly reduced EAC risk among ever drinkers (RR=0.78, 95%CI: 0.64, 0.96), Fahey *et al.* did not find a significant association (RR=1.08, 95%CI: 0.85, 1.37)[28]. Another study reported a borderline non-significant association when comparing drinkers with non-drinkers[35]. Although point estimates globally increased with alcohol consumption, no significant associations were found in most meta-analyses, even at high levels of consumption[23, 28, 31, 35]. An exception was the subgroup analysis reported by Freedman *et al.*[29] regarding the type of drink, in which drinking up to one glass of wine per day was found reducing the risk of EAC in comparison with non-drinkers. For individuals without GERD, EAC risk was found approximately 50% lower among drinkers than among non-drinkers, regardless of the number of drinks consumed per day[29]; this reduced risk was also observed in a more recent meta-analysis, in the overall analysis and in the age group ≥ 70 years old[34].

Tobacco smoking

Fourteen studies evaluated the association between tobacco smoking and EC, EAC or ESCC[17, 23, 26-28, 31, 32, 34, 36-41]. Using never smokers as the reference category, results obtained from the five studies not providing histology-specific RRs yielded no significant differences between sexes, study designs (case-control and cohort studies), ethnicities (African-Americans, Asians and Caucasians, though Asians had a lower point estimate), geographical areas (Western and Non-Western countries), smoking habits (former, current and ever smokers) or adjustment (or not) for alcohol consumption[17, 36, 37, 39, 40]. A substantially higher risk of EC was found among drinkers (RR=6.01, 95%CI: 3.82, 9.44) than among non-drinkers (RR=2.45, 95%CI: 2.06, 2.91), when comparing current with never smokers[36]. Overall, an increment of 100 g/week of tobacco consumption was found to increase the risk of EC by 32% (RR=1.32, 95%CI: 1.15, 1.52)[23]. Six meta-analyses focused on tobacco smoking and ESCC (Figure 3A)[23, 26-28, 31, 32]. Current smokers had a significantly higher risk of ESCC than never smokers (RR=5.1 among men, RR=3.1 among women)[26] and presented twice the risk of former smokers (RR=3.13, 95%CI: 2.53, 3.86 vs. RR=1.68, 95%CI: 1.44, 1.96)[32]. An increment of 100 g/week of tobacco consumption was found increasing ESCC overall risk by 25%[23]. Dose-response effects were reported with the number of cigarettes smoked per day (cig/day)[26], the number of smoking years[26] and the number of pack-years[28, 31], using non-smokers as reference. People who had started smoking after they were 21 years old had a significantly lower risk of ESCC than those aged 13 or younger at smoking onset

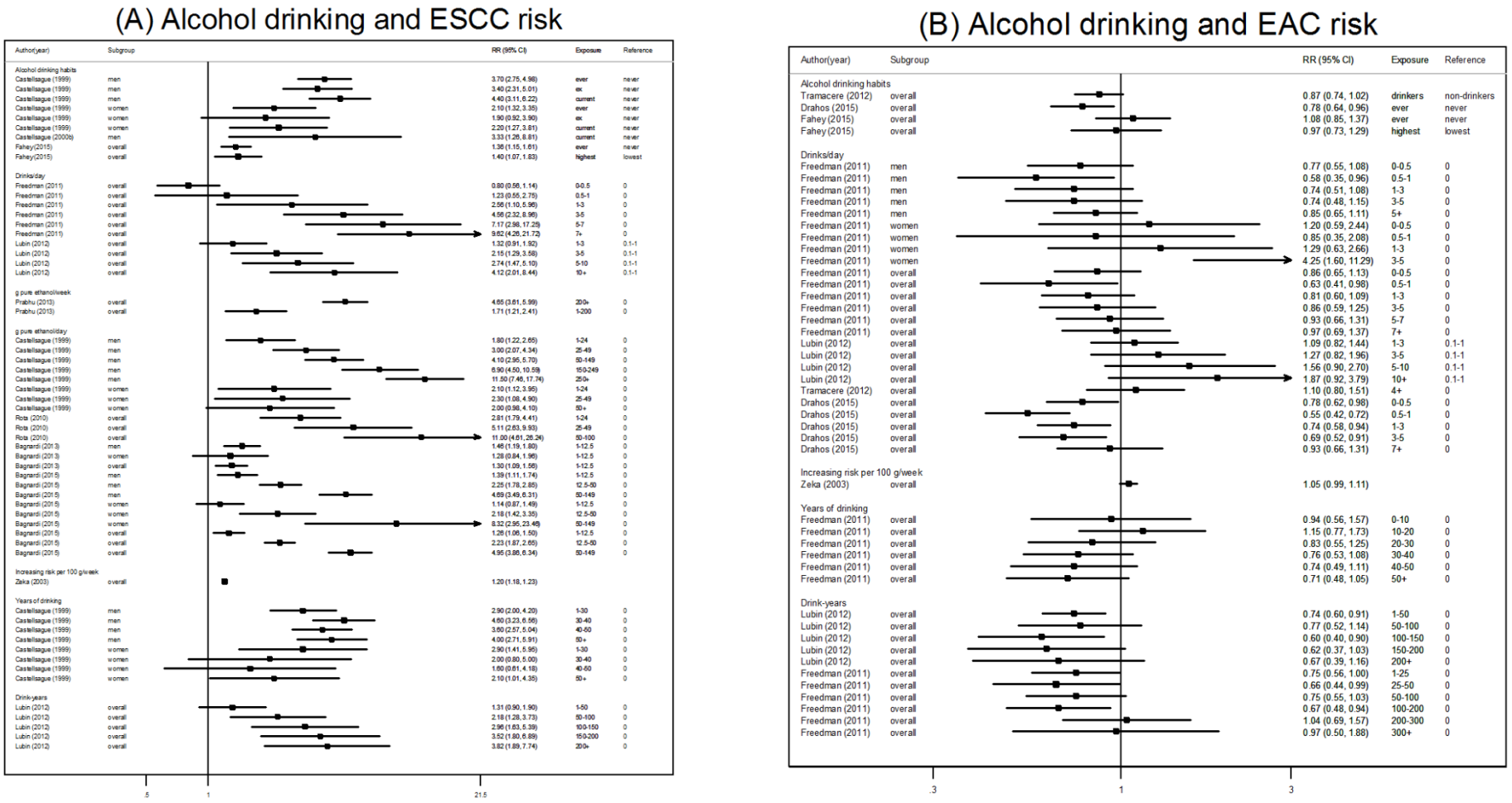

Figure 2: Forest plots of overall and sex-specific associations between alcohol drinking and the occurrence of: (A) esophageal squamous cell carcinoma (ESCC); (B) esophageal adenocarcinoma (EAC). RR: relative risk, CI: confidence interval.

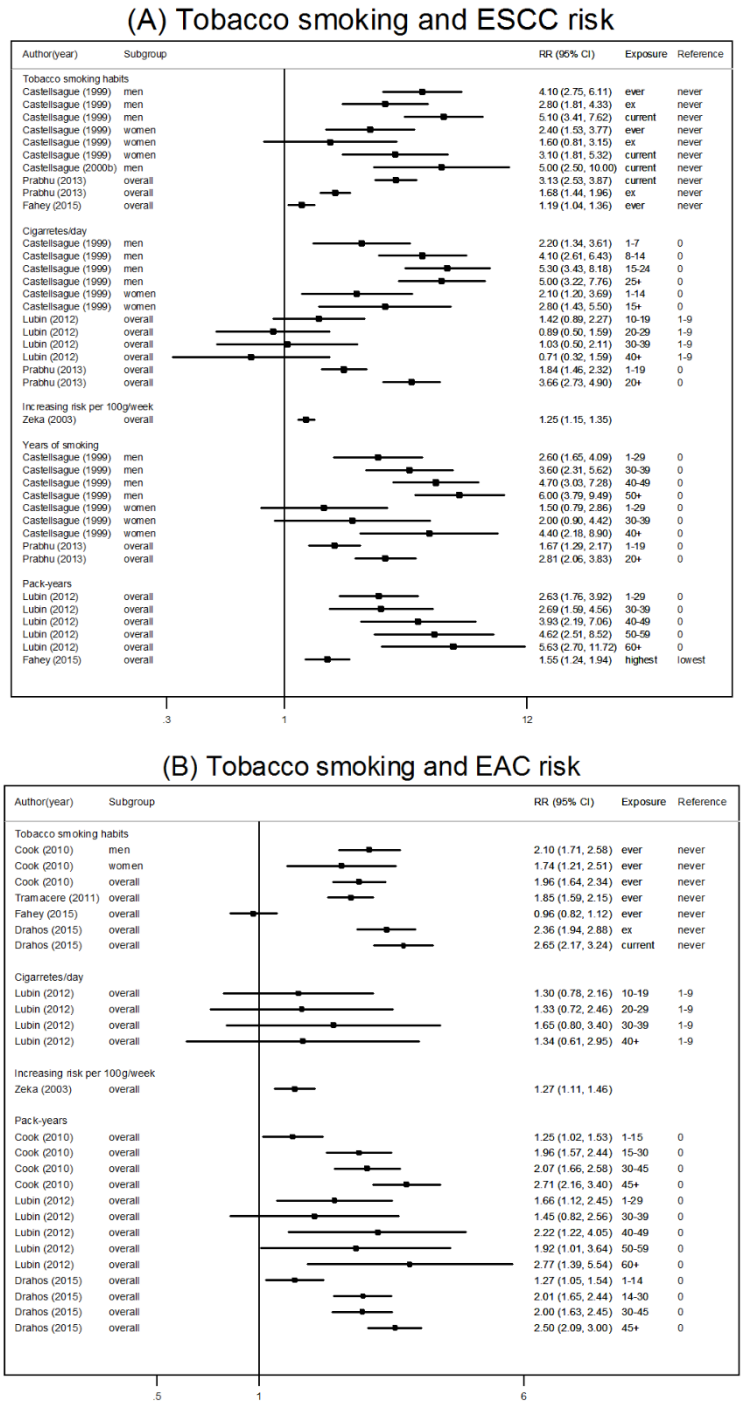

Figure 3: Forest plots of overall and sex-specific associations between tobacco smoking and the occurrence of: (A) esophageal squamous cell carcinoma (ESCC); (B) esophageal adenocarcinoma (EAC). RR: relative risk, CI: confidence interval.

(RR=0.6 among men and RR=0.2 among women)[26]. Prabhu *et al.*[32] found a lower ESCC risk in Asia (RR=2.31, 95%CI: 1.78, 2.99) than in Europe (RR=4.21, 95%CI: 3.13, 5.66) when comparing current with never smokers.

Six studies reported the association between tobacco smoking and EAC (Figure 3B)[23, 28, 31, 34, 38, 41]. The only meta-analysis providing sex-specific estimates showed a non-significantly higher EAC risk among men (RR=2.10 for men, RR=1.74 for women)[38], with the strength of association being much lower than that of ESCC. As for ESCC, an increasing EAC risk was found with an

increment of 100 g/week of tobacco consumption (RR=1.27, 95%CI: 1.11, 1.46)[23] and with the number of pack-years[31, 34, 38]. When comparing ever with never smokers, the association between smoking and EAC was found significant in two meta-analyses(RR≈1.9)[38, 41], but not in a third one (RR=0.96, 95%CI: 0.82, 1.12, n=4)[28]. Drahos *et al.*[34] performed an age-specific analysis and found a significant association of both current and former smoking with the risk of EAC, for all age groups; the highest estimates were observed for ages 50-59 years (RR=3.75 for current and RR=2.95 for former smokers) and the lowest for ages 60-69 years (RRs of 1.81 and 1.86, respectively).

Alcohol drinking/tobacco smoking cessation

Time since cessation of alcohol drinking (Supplementary Figure 2A) or tobacco smoking (Supplementary Figure 2B) was assessed in four meta-analyses[26, 27, 42, 43]. For EC as a whole, using current drinkers as the reference category, the RRs obtained for never drinkers and the group of 15 or more years since drinking cessation were similar (RR=0.37) and did not relevantly change after adjustment for smoking[43]. In 2012, a comparison between the longest cessation group and current drinkers yielded a RR=0.46 (95%CI: 0.34, 0.63)[42].

Ten or more years since cessation did not suffice to reduce ESCC risk to the values observed among never drinking men nor among never smoking men; among women, five and ten years since cessation were enough to reach similar values to the ones obtained for never drinkers and never smokers, respectively[26]. Male drinkers who had quitted between the ages of 48 and 57 had a significantly higher ESCC risk than those quitting before they were 48 years old; otherwise, age at quitting drinking or smoking did not significantly change ESCC risk[26]. The risk of ESCC among men was shown to decrease by 4% per year since cessation of alcohol drinking (RR=0.96, 95%CI: 0.94, 0.98) and by 2% per year since cessation of tobacco smoking (RR=0.98, 95%CI: 0.97, 0.99)[27]. No meta-analyses were found on the association between alcohol drinking cessation or tobacco smoking cessation and EAC.

Waterpipe smoking and smokeless tobacco

Akl *et al.*[44] reported a higher risk of EC among current waterpipe smokers, in comparison with never smokers, although this association was not statistically significant (RR=1.85, 95%CI: 0.95, 3.58) and it was based on a single observational study. Akhtar *et al*.[45] performed the only meta-analysis focusing on areca nut (also commonly referred to as betel nut) chewing, and reported an increased risk of ESCC for chewers in comparison with non-chewers (RR=3.05, 95%CI: 2.41, 3.87); the risk estimate provided did not relevantly change when considering only men nor when adjusting for education, tobacco chewing, alcohol drinking or fruit and vegetable intake.

Among never tobacco smokers, the use of snus (a moist powder tobacco product originating from a variant of dry snuff, and consumed by placing it under the upper lip for extended periods

of time) significantly increased the risk of ESCC (RR=3.5, 95%CI: 1.6, 7.6) and reduced, though not significantly, the risk of EAC (RR=0.2, 95%CI: 0.0, 1.9)[46].

The effects of smokeless tobacco, including any form of chewing tobacco, oral snuff, snus or tobacco pastes or powders, have been assessed by three meta-analyses[47-49]. In 2008, Boffeta *et al*.[47] reported an increased risk of EC among ever users in comparison with never users (RR=1.6, 95%CI: 1.1, 2.3), with significant results in Nordic countries (four studies), but not in the United States of America (USA) (one study). In 2009, Lee *et al*.[48] reported summary point estimate lower than the one previously found (RR=1.25; 95%CI: 1.03, 1.51), which was significant in the USA (six studies), but not in Nordic countries (using the same four studies, but with a different combination of results). When adjusting for tobacco smoking, there was no significant association between smokeless tobacco and the risk of EC (RR=1.13, 95%CI: 0.95, 1.36), while there was a higher EC risk among never smokers (RR=1.91, 95%CI: 1.15, 3.17)[48]. In 2015, Siddiqi *et al.*[49] reported a significantly higher risk of EC among ever smokeless tobacco users, in comparison with never users (RR=2.17, 95%CI: 1.70, 2.78), which remained significant when restricting the analysis to studies performed in India (n=7), Pakistan (n=2) and Sweden (n=5), but not in Norway (n=1) and North America (n=1).

H. pylori infection

The effect of HP infection was evaluated by five meta-analyses that reported results for both ESCC and EAC (Figure 4)[50-54]. All reported similar results, showing no association between HP and ESCC, while for EAC a protective effect of HP infection was found (RR≈0.5). When comparing cytotoxin-associated gene A (CagA) positive strains with CagA negative strains, results were similar[51, 53]. However, in 2013, protective effects of both HP infection (RR=0.66, 95%CI: 0.43, 0.89) and CagA positive strains (RR=0.77, 95%CI: 0.65, 0.92) were found regarding ESCC risk when the analyses were restricted to studies from Iran and China[52].

GERD symptoms

The association between GERD symptoms and EAC has been assessed by three meta-analyses, which reported a gradually increased risk of EAC with the increasing frequency and duration of GERD symptoms[34, 55, 56]. Patients with weekly symptoms presented an EAC risk of 4.92 (95%CI: 3.90, 6.22) when compared to individuals with less than weekly frequency or no symptoms, which rose to 7.40 (95%CI: 4.94, 11.10) when patients had daily symptoms[55]. Less than 10 to 15 years of symptoms duration yielded an EAC risk of 3.05 (95%CI: 1.53, 6.08), while more than 20 years in duration presented a risk of 5.41 (95%CI: 2.45, 11.9)[55]. RRs were generally lower for regurgitation (e.g., RR=4.94 for daily regurgitation vs. RR=7.42 for daily heartburn, when

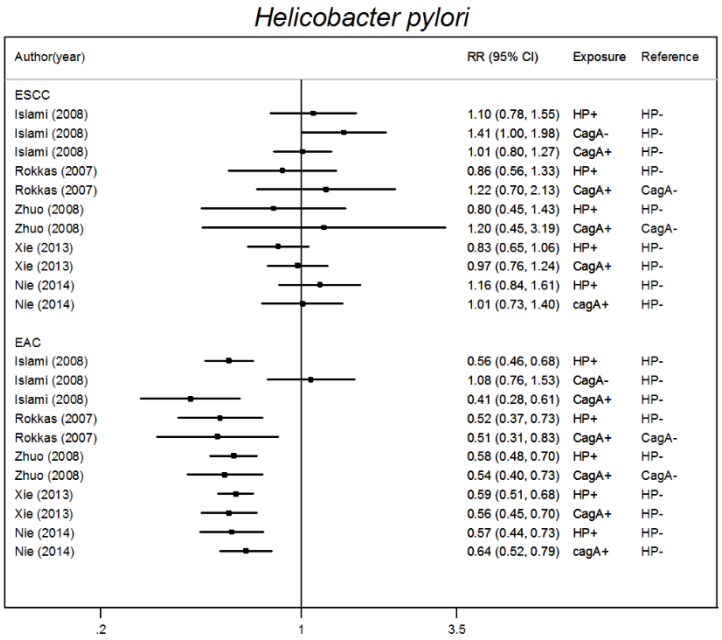

Figure 4: Forest plot of overall association between *H. pylori* and the occurrence of esophageal cancer, by histological subtype. RR: relative risk, CI: confidence interval, ESCC: esophageal squamous cell carcinoma, EAC: esophageal adenocarcinoma.

compared to individuals with no symptoms)[56]. When comparing more than daily with no symptoms, individuals aged 50-59 presented the lowest estimates (RR=4.65 for heartburn and RR=3.25 for regurgitation), while individuals aged less than 50 or over 70 presented the highest values (RR=6.84 and 11.41 for heartburn, and RR=7.00 and RR=6.58 for regurgitation, respectively)[34].

Barrett's Esophagus

Only one meta-analysis focused this risk factor, showing a non-significantly decreased EAC risk among individuals with short segment Barrett's Esophagus when compared to conventional Barrett's Esophagus (RR=0.55, 95%CI: 0.19, 1.50)[57].

BMI

Twelve publications assessed BMI (Supplementary Figure 3), one of which did not provide histology-specific RRs[58]. ESCC was focused by four meta-analyses[22, 28, 59, 60]. No significant change was found in ESCC risk with an increment of 1 kg/m^2[22], but a significant reduction was found with an increment of 5 kg/m^2 (RR=0.71 for men and RR=0.57 for women)[59]. This protective effect remained when performing analysis by study design, with a significantly lower RR being found in case-control studies (RR per 5 kg/m^2=0.49, 95%CI: 0.44, 0.55) than in cohort studies (RR=0.69, 95%CI: 0.63, 0.75)[60]. In 2015, a significantly reduced ESCC risk was found among individuals with a BMI over 25 (RR=0.8, 95%CI: 0.67, 0.95), but not among obese individuals (RR=1.05, 95%CI: 0.76, 1.46), when compared to a normal weight[28].

EAC was focused by 11 studies, eight of which reported a significant dose-response effect of BMI [22, 34, 59-64]. In 2013, EAC risk was found increasing by 13% per 5 kg/m^2 (RR=1.13, 95%CI: 1.11, 1.16)[64], and a RR of 2.51 (95%CI: 1.56, 4.04) was reported when comparing the highest with the lowest category of central adiposity[65]. However, non-significant associations were found when comparing obese with normal weight men (RR=1.23, 95%CI: 0.58, 2.60)[66], or when restricting analyses to individuals aged less than 50 (RR=1.64, 95%CI: 0.99, 2.73) or older than 70 years old (RR=1.19, 95%CI: 0.93, 1.52), in the comparison between overweight and normal weight individuals[34].

Physical activity

Five meta-analyses were published, between 2014 and 2015, focusing the association between physical activity or sedentarism and the occurrence of EC[28, 67-70], one of which did not provide histology-specific estimates[69]. The remaining four meta-analyses compared the highest with the lowest levels of exercise, finding no significant association with ESCC[28, 67, 68, 70]. Two meta-analyses found a significant protective effect of physical activity on EAC risk (RR=0.79, n=7[67] and RR=0.68, n=4[70]), while the other two found no significant association[28, 68].

Further stratified results were only available for EC as a whole. A significantly reduced risk of EC was reported for studies from North America (RR=0.77, 95%CI: 0.64, 0.92), Australia (RR=0.72, 95%CI: 0.57, 0.91) and Middle East (RR=0.48, 95%CI: 0.29, 0.81)[67], but not from Europe or Asia[67, 68, 70]. A reduced risk of EC was also reported among men and women, and in both case-control and cohort studies[67, 68, 70].

Diet

No significant changes in ESCC risk were found regarding dietary glycemic index[71, 72]. In 2009, Mulholland *et al.* [71] reported a significantly increased ESCC risk per 100 units/day of glycemic load (RR=1.2), based in a single case-control study; in 2015, a meta-analysis based on four studies showed a lack of association when comparing the highest with the lowest categories of glycemic load[72]. In 2012, Yu *et al.*[73] found no significant association between energy intake and EC. In 2014, when comparing the highest with the lowest levels of intake, ESCC risk was significantly reduced among individuals presenting a healthy dietary pattern (described as a higher loading of fruits, fresh vegetables, dietary fiber and antioxidants and a lower loading of fat dairy, processed food and meat) (RR=0.36) and increased for an alcohol dietary pattern (RR=2.34), while it did not significantly change for a western dietary pattern (higher loading of fat, animal food and processed food, and a lower loading of fruits, vegetables, and dietary fibres)[74]. No similar meta-analyses were found regarding EAC.

Four meta-analysis on fruits and/or vegetables did not report histology-specific estimates[22, 75-77]. ESCC risk was reduced by 40% to 60% when the highest intake of fruits or vegetables was

compared to the lowest intake[78, 79], with no significant associations being found among women[78] (Supplementary Figure 4). Regarding fruit consumption, ESCC risk was significantly lower in Europe and in South America (RR≈0.4) than in Asia (RR=0.67), while for vegetable consumption it was significantly lower in Europe (RR=0.3) than in Asia, South America and the USA (RR≈0.65)[79]. An increment of 100g/day of fruit intake was found decreasing ESCC risk by nearly 40%, while an increment of 100g/day in vegetable consumption reduced it by 16%[79]; for EAC, corresponding values were of 13% and 9%, respectively[80]. Increasing intakes of 50g/day of citrus fruits, raw vegetables and non-starchy vegetables were found decreasing EC risk by 30%, 31% and 13%, respectively[22], while the consumption of pickled vegetables was found doubling ESCC risk (RR=2.08, 95%CI: 1.66, 2.60), when compared to no or low consumption[81].

When comparing the highest with the lowest category of intake, no significant associations were found for ESCC with the consumption of meat (overall[82, 83] and among women[78]), barbecue[78], cereals[78], fat (among women)[78], fiber[84], salt (among women)[78], acrylamide[85, 86], zink[87], beta-carotene [88], green tea[89], coffee[78, 89, 90], coffee with milk[78] and soft drinks[91]. Using the same categories of exposure, a significantly increased ESCC risk was found regarding the consumption of meat (RR=1.46, 95%CI: 1.11, 1.92 among men)[78], red meat (RRs between 1.55 and 1.86)[82, 83, 92, 93], fat (RR=1.57 among men)[78], salt (RR=2.11 among men)[78], while a significantly decreasing ESCC risk was reported regarding the consumption of white meat (RR=0.63)[83], folate (RR≈0.65)[94, 95], alpha-carotene (RR=0.82)[88], beta-cryptoxanthin (RR=0.83)[88], lycopene (RR=0.74)[88] and tea (RR=0.53 among men)[78]. In 2014, a meta-analysis on poultry consumption found a significantly reduced ESCC risk (RR=0.73)[83] when comparing the highest with the lowest total meat consumption, which had not been reported in a previous study[82]. For red meat, a dose-response effect was found per increasing 100 g/day (RR=1.41, 95%CI: 1.16, 1.70)[93]. Three meta-analyses evaluated the association between fish and ESCC: while one of them found a significant protective effect in the overall analysis, based on 17 studies, when comparing the highest with the lowest categories of intake (RR=0.81, 95%CI: 0.66, 0.99)[96], the other two found no significant association[82, 83]. The association between processed meat and ESCC was assessed by four meta-analyses published between 2013 and 2014: three of them[82, 83, 92] yielded an increasing though not significant association in the overall analysis, while the fourth one[93] presented a RR of 1.55 (95%CI:1.22, 1.97) when comparing the highest with the lowest categories of intake and found a significant dose-response effect per increasing 50 g/day of processed meat intake on ESCC risk (RR=1.81, 95%CI: 1.32, 2.48)[93]. A significant dose-response effect was found between the consumption of maté and the occurrence of ESCC[78, 97]; the association between maté drinking and ESCC was found stronger among women than men, and no significant differences were found between people who had quitted drinking maté for 10 or more years and never drinkers[78].

For EAC, no significant associations were found with the consumption of poultry[82, 83], white meat[83], fish[82, 83, 96], acrylamide[85, 86], zink[87], vitamin E[98], coffee[89, 90] and soft drinks[91], while a decreasing risk was found regarding folate (RR≈0.5)[94, 95], fiber (RR=0.66)[84], beta-carotene

(RR=0.46)[88, 98] and vitamin C intake (RR=0.49)[98] and an increasing risk was reported with the consumption of total meat (RR=1.96)[83], red meat (RR between 1.2 and 1.4)[82, 83, 92, 99] and processed meat (RR≈1.4)[82, 83, 92, 99].

No significant associations for EC were found with barbecued meat[82], eggs[22], milk and dairy products[22], acrylamide[85] and black tea[89] consumption, while a protective effect was found regarding white meat (RR=0.71)[82], fish (RR=0.91)[100], folate (RR=0.6)[101] and lutein and zeaxanthin intake (RR=0.71)[88]. While a meta-analysis found a significant protective effect of coffee for EC (RR=0.55)[102], a more recent study yielded no significant association, except among Asian results (RR=0.67)[89]. A decreasing EC risk was also found regarding green tea consumption among women (RR between 0.32 and 0.46[89, 103, 104]), but not among men or in the overall analysis[17, 89, 103, 104].

EC risk increased with the consumption of hot/very hot beverages (RR=1.77) and foods (RR=2.09)[105]. This association was also found significant for ESCC (RR=1.6, 95%CI: 1.29, 2.00), but not for EAC (RR=0.79, 95%CI: 0.53, 1.16)[105]. Restricting the analyses to the type of drink, a significantly increasing risk of ESCC was found when comparing very hot to cold/warm maté (RR=1.77 for men and RR=2.47 for women), tea (RR=8.73 for men and RR=2.20 for women) and coffee with milk among men (RR=2.22), while no significant associations were found for coffee (both sexes) and coffee with milk (for women)[78].

Interactions between risk factors

Seven studies evaluated the interaction between some of the aforementioned risk factors for EC, EAC or ESCC[4, 17, 26, 36, 45, 62, 78]. For ESCC, significant interactions were found between areca nut chewing and tobacco smoking (RR=6.79, 95%CI: 4.71, 9.79)[45], tobacco smoking and alcohol drinking (RR=3.28, 95%CI: 2.11, 5.08)[4] and between the consumption of maté at very hot temperatures and drinking more than 1.5 liters of maté per day (RR=4.14, 95%CI: 2.24, 7.67)[78].

For EAC, a significant interaction was found between overweight/obesity (BMI≥27.5 kg/m^2) and the presence of GERD symptoms (RR=3.18, 95%CI: 2.45, 4.13)[62], but no modifying effects were found between overweight/obesity and cigarette smoking or alcohol drinking.

Ishikawa *et al.*[17] evaluated the potential effect modifications of smoking (current), alcohol (daily) and green tea (≥3 cups/day) consumption on EC risk, by analyzing combined categories of these variables and using people with none of the exposures as reference. The interactions between smoking and alcohol drinking, smoking and green tea consumption, alcohol and green tea consumption and all three variables yielded RRs of 9.23 (95%CI: 2.10, 40.60), 4.99 (95%CI: 1.11, 22.43), 2.97 (95%CI: 0.53, 16.58) and 11.10 (95%CI: 2.63, 46.51), respectively. Ansary-Moghaddam *et al.*[36] also evaluated the interaction between smoking and alcohol, using 15 studies, and obtained a RR of 10.0 (95%CI: 4.08, 24.50) for EC.

DISCUSSION

The association between the most well-known risk factors for esophageal cancer and its occurrence have been extensively described in the literature and an increasing number of meta-analyses have been published focusing those determinants. The risk of ESCC increased with alcohol and maté drinking, tobacco smoking and with red and processed meat consumption, while it was negatively associated with body mass index and the consumption of fruit, vegetable, white meat, folate and some carotenoids. For EAC, a significantly increased risk was reported for tobacco smoking, body mass index, increasing frequency and duration of gastroesophageal reflux symptoms and red and processed meat consumption, while it was reduced by *Helicobacter pylori* infection, low/moderate alcohol drinking, physical activity and the consumption of fruit, vegetables, folate, fiber, beta-carotene and vitamin C.

To the best of our knowledge, this is the first systematic review of meta-analyses on esophageal cancer environmental risk factors. Although methodological limitations are inherent to the primary studies included in the meta-analyses, this review depicts the state of the art on the modifiable risk factors for EC, showing marked differences between its subtypes regarding the strength of association with each determinant.

When a meta-analysis was published regarding a risk factor, a new meta-analysis on the same determinant usually yielded further stratified results, or it was based on a different set of observational studies (e.g., from a different geographical area). In most situations, risk estimates did not differ significantly between meta-analyses focusing on the same risk factors, but there were some exceptions which should be discussed.

Most meta-analyses found no significant association between alcohol drinking and EAC, even at high levels of consumption. However, two meta-analyses, originated from pooled analysis of studies included in the International Barrett's and Esophageal Adenocarcinoma Consortium (BEACON), suggested a protective effect of low/moderate alcohol consumption on EAC risk[29, 34]. In 2011, based on nine case-control and two cohort studies, Freedman *et al.*[29] suggested that modest alcohol drinking, particularly less than one drink per day, might be associated with reduced EA risk. Although the inverse associations found could be due to chance (the stratification of results led to a small number of cases in each strata) or recall bias (since most of the included studies were of case-control design), the authors argued that these results could also depict a true association, as alcohol consumption may have favorable effects on insulin resistance or levels of serum lipids and lipoproteins[106], which may be important for EAC risk. In 2015, two meta-analyses compared ever with never drinkers: while Drahos *et al.*[34] found a significant protective effect of alcohol consumption on EAC risk, at all ages and in people aged 70 or older, Fahey *et al.*[28] found no significant association. Although results obtained by Fahey *et al.* were based on a systematic review, only two case-control studies (from Sweden and the USA) were used to obtain the summary estimates, while Drahos *et al.* used individual data from

8 BEACON case-control studies (from Australia, Ireland, Sweden and the USA). Therefore, results provided by the latter are more reliable, since a larger number of studies was included in the analysis, and the usage of individual data allows for the adjustment of each study's results to the same variables, ensuring the comparability of results.

Tobacco consumption was found significantly increasing EAC risk in all meta-analyses, with the exception of Fahey *et al.*[28], who compared ever with never smokers, based on 4 studies, and found no significant association. As before, this lack of association is probably due to the smaller number of studies included in the meta-analysis, in comparison with the other studies performing similar evaluations[34, 38, 41].

For smokeless tobacco, the conflicting results found between Boffetta *et al.*[47] and Lee and Hamling[48] were discussed in a commentary[107] which concluded that the latter results were more reliable, as authors included a larger number of studies, used smoking-adjusted estimates whenever possible and, for studies where the RR was not provided but could be derived from data, they calculated an estimate of the effect measure, instead of excluding those papers. Those results were also more reliable than the ones provided in a more recent meta-analysis, which presented a higher RR but found a high degree of heterogeneity (I^2=76%) between the studies included in the analysis[49].

Two meta-analyses[67, 70] found an inverse association between physical activity and EAC risk, while two other[28, 68] found no significant association. As before, the meta-analyses which did not provide a significant result were the ones including the smaller number of studies in the analyses (only two observational studies included in each). Proposed mechanisms for the protective effect of physical activity on cancer are that it may prevent carcinogenesis by reducing insulin resistance and lowering fasting insulin levels, increasing the concentration of anti-inflammatory adipocytoxines [108], decreasing oxidative stress and enhancing DNA repair[109].

In all meta-analyses found in our study, HP infection was consistently described as having a protective effect of EAC risk, while no significant association was found with ESCC. The mechanisms underlying the inverse association between HP infection and EAC are not clear, but it has been suggested that hypoacidity in association with gastric atrophy may have a role[110].

GERD is one of the most commonly mentioned risk factors for EAC in epidemiological studies, but few meta-analyses have focused this determinant. A strong association between GERD symptoms and EAC has been described, with estimated ORs ranging from 5 to over 40[8, 111], a variability that reflects the increase in risk with the duration, frequency and severity of symptoms. The high heterogeneity between studies, which has also been reported in the meta-analyses included in our study, may explain why most reviews on GERD symptoms do not provide summary estimates.

Overweight and obesity were consistently reported as risk factors for EAC, but a protective effect of BMI was found regarding ESCC. Overweight and obesity have been proposed to increase reflux, causing chronic inflammation and Barrett's Esophagus, which predisposes to EAC[112].

However, studies have shown that only a small proportion (≈5%) of EAC cases are previously diagnosed with Barrett's Esophagus, and that patients with this condition rarely develop EAC[113]. Furthermore, both independent and synergistic effects of BMI and GERD have been reported[62], which means that other mechanisms are also in place. The systemic inflammatory state led by the altered metabolism of obese patients, and the associated impact of adipocytokines and pro-coagulant factors released by adipocytes in central fat, has been a proposed explanation for obesity's association with EAC[114]. Some authors have argued that the observed inverse association between BMI and ESCC is real, though not necessarily causal[59, 60]. Since a high consumption of fruit and vegetables and the adoption of healthy dietary patterns have also been reported to be inversely associated with ESCC, it has been proposed that a low calorie diet which lowers BMI is likely to be restricted in micronutrients, and these deficiencies could lead to increased risk of ESCC[60]. Another possible explanation is a negative confounding of the BMI and cancer association by smoking intensity[115], which has been supported by studies presenting an inverse association between BMI and ESCC risk among smokers, but not among non-smokers[116].

Although our quality assessment of included studies has shown that most meta-analyses published regarding EC risk factors are of good quality, the key limitation on the interpretability of our findings is the heterogeneity between (and within each of) the meta-analyses selected for inclusion in our review. Among the 95 selected studies, 81 were performed following a systematic review of literature, 12 were obtained through pooled analysis and 2 did not clearly state the inclusion criteria. Among the studies conducting systematic reviews, some focused on a specific geographical area (e.g., Japan[20, 40]) or included only studies of a given design (e.g., cohort studies[100, 102]); 6 of the pooled analyses used data from BEACON, 3 used data from studies conducted in South America, 2 in Asia and 1 in Italy. Thus, cultural aspects, customs and lifestyles of each geographical area are likely explanations for the differences found between summary estimates provided for some determinants, namely regarding diet. Out of the 51 meta-analysis found for EC, 32 did not provide histology-specific estimates, even though 12 of those studies specifically focused EC as an outcome of interest, while the others targeted digestive cancers, neoplasms in general and other public health outcomes such as cardiovascular diseases, presenting EC as an accessory result. Furthermore, moderate to high degrees of heterogeneity were observed in several of the studies included in our review, even when performing stratified analyses by sex, geographical area or study design. In fact, many authors have mentioned the difficulties in performing stratified meta-analyses using available data from observational studies, since there is no standardization in data collection and data reporting[28, 115].

Our study has shown that a significant reduction in ESCC risk could be obtained from alcohol drinking and tobacco smoking cessation, with RRs reaching similar values to the ones observed in individuals who never drank or smoked, within some years after cessation. This depicts the importance of planning interventions aimed to reduce the consumption of both alcohol and tobacco. Future studies focusing on EAC to provide such estimates would also be useful,

especially given the marked increase in EAC incidence trends observed in Western countries in the last decades[1, 117].

Our inclusion criteria led to the exclusion of many studies focusing on medications (e.g., nonsteroidal anti-inflammatory drugs), treatments and genetic factors. Future reviews on these factors could yield relevant information on the etiology of EC, namely through the evaluation of confounding/synergistic effects with the determinants we have included in our work. There are some comorbidities which have also been assessed through meta-analyses and may be worth analyzing in future studies. Examples include an increased risk of ESCC found in people with gastric atrophy (RR=1.94, 95%CI: 1.48, 2.55)[118] and in Human Papiloma Virus seropositive individuals (for HPV16 E6, HPV6 L1, HPV6 E6§ and HPV11 L1 subtypes)[119], and an increased risk of EAC in the presence of diabetes mellitus (RR=2.12, 95%CI: 1.01, 4.46)[120].

In conclusion, this comprehensive systematic review summarizes the state of the art on the etiology of EC, showing evident differences between ESCC and EAC regarding some risk factors. This reinforces the importance of a separate assessment of EC subtypes to allow for a proper discussion of incidence trends and a suitable planning of interventions towards the reduction of cancer burden in the population.

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CONFLICTS OF INTEREST

None to disclose.

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Supplementary Table 1: Description of the Meta-analyses Included in the Systematic Review.

First author, year (ref)	Outcome (measures)	Databases searched (time period)	Search expression / terms Search restrictions	Number and type of studies included, when available	Quality score assessment	Summary estimate (95% CI) Heterogeneity (I^2 and sources) Publication bias
ALCOHOL						
Holman, 1996[16]	EC (mortality)	MEDLINE (1980-1994) Citation tracking	Not stated Restricted to studies published in English and study populations primarily of European origin	7	No	Responsible (0-2.9 drinks/day) *vs.* Abstinence RR=1.80 (1.63-1.99), n=7 Hazardous (3-4.9 drinks/day) *vs.* Abstinence RR=2.37 (2.03-2.76), n=7 Harmful (≥5 drinks/day) *vs.* Abstinence RR=4.26 (3.70-4.90), n=7
Castellsagué, 1999[26]	ESCC (risk)	Pooled analysis of hospital-based case-control studies conducted in high-risk areas in South America	NA	5 case-control	NA	Ever *vs.* never drinkers Men – OR=3.7 (2.7-4.9) Women – OR=2.1 (1.3-3.3) Current *vs.* never drinkers Men – OR=4.4 (3.1-6.2) Women – OR=2.2 (1.3-3.9) Ex- *vs.* never drinkers Men – OR=3.4 (2.3-5.0) Women – OR=1.9 (0.9-3.8) Average amount of pure ethanol/day (ml) *Men* 1-24 – OR=1.8 (1.2-2.6) 25-49 – OR=3.0 (2.1-4.4) 50-149 – OR=4.1 (3.0-5.8) 150-249 – OR=6.9 (4.5-10.6) ≥ 250 – OR=11.5 (7.4-17.6) *Women* 1-24 – OR=2.1 (1.1-3.9) 25-49 – OR=2.3 (1.1-5.0) ≥ 50 – OR=2.0 (1.0-4.2) Years of alcohol drinking *Men* 1-29 – OR=2.9 (2.0-4.2) 30-39 – OR=4.6 (3.2-6.5) 40-49 – OR=3.6 (2.6-5.1)

			≥ 50 – OR=4.0 (2.7-5.9) *Women* 1-29 – OR=2.9 (1.4-5.9) 30-39 – OR=2.0 (0.8-5.0) 40-49 – OR=1.6 (0.6-4.1) ≥ 50 – OR=2.1 (1.0-4.3) <u>Age at starting drinking</u> *Men* 17-19 – OR=1.1 (0.8-1.5) 20-24 – OR=0.9 (0.7-1.3) ≥ 25 – OR=0.9 (0.7-1.3) *Women* 17-24 – OR=1.1 (0.4-3.0) ≥ 25 – OR=1.1 (0.4-3.4) <u>Age at quitting drinking</u> *Men* 48-57 – OR=2.2 (1.1-4.6) 58-65 – OR=2.2 (1.0-5.0) ≥ 66 – OR=1.0 (0.4-2.6) *Women* ≥ 58 – OR=1.8 (0.2-14.4) <u>Years since quitting drinking</u> *Men* 1-4 – OR=0.9 (0.7-1.3) 5-9 – OR=0.8 (0.5-1.4) ≥ 10 – OR=0.6 (0.4-0.9) *Women* 1-4 – OR=1.3 (0.4-4.4) ≥ 5 – OR=0.6 (0.2-1.8) <u>Type of drink</u> *Men* Ever beer – OR=2.6 (1.8-3.8) Ever wine – OR=3.5 (2.6-4.8) Ever spirits – OR=4.5 (3.3-6.1) *Women* Ever beer – OR=5.5 (1.6-19.5) Ever wine – OR=1.6 (1.0-2.7) Ever spirits – OR=8.0 (2.7-23.9)

Corrao, 1999[14]	EC (risk)	MEDLINE (1966-1998) Citation tracking	Not stated	14 1 cohort 13 case-control	Questions related to the study design, alcohol consumption data collection methods and data analysis were used to obtain quality score.	<u>Dose-response analysis</u> ACCORDING TO GEOGRAPHIC AREA *Mediterranean* 25 g/day – RR=1.6 (1.5-1.7) 50 g/day – RR=2.5 (2.2-2.8) 100 g/day – RR=6.0 (4.6-7.8) *Other areas* 25 g/day – RR=1.5 (1.3-1.7) 50 g/day – RR=2.2 (1.7-2.8) 100 g/day – RR=4.5 (2.6-7.8)
Bosetti, 2000[13]	EC (risk)	Pooled analysis of two case-control studies conducted in the greater Milan area and in the province of Pordenone, in northern Italy, between 1984 and 1998	NA	2 case-control	NA	<u>Total alcohol, according to the number of drinks/day</u> 3-4 *vs.* 1-2 – OR=1.98 (1.46-2.67) 5-7 *vs.* 1-2 – OR=4.22 (3.10-5.75) 8-11 *vs.* 1-2 – OR=7.60 (5.51-10.48) ≥ 12 *vs.* 1-2 – OR=12.35 (8.37-18.21) <u>Wine only, according to the number of drinks/day</u> 3-4 *vs.* 1-2 – OR=1.70 (1.14-2.54) 5-7 *vs.* 1-2 – OR=4.21 (2.69-6.58) 8-11 *vs.* 1-2 – OR=8.76 (5.37-14.27) ≥ 12 *vs.* 1-2 – OR=17.90 (6.56-48.85) <u>Wine and other, according to the number of drinks/day</u> 3-4 *vs.* 1-2 – OR=1.83 (1.20-2.79) 5-7 *vs.* 1-2 – OR=3.50 (2.34-5.25) 8-11 *vs.* 1-2 – OR=6.01 (3.97-9.11) ≥ 12 *vs.* 1-2 – OR=10.00 (6.30-15.87) <u>Beer, according to the number of drinks/day</u> 1-2 *vs.* 0 – OR=0.96 (0.75-1.23) ≥ 3 *vs.* 0 – OR=1.35 (0.91-1.99) <u>Spirits, according to the number of drinks/day</u> 1-2 *vs.* 0 – OR=0.99 (0.79-1.23) ≥ 3 *vs.* 0 – OR=1.51 (0.95-2.38)
Castellsagué, 2000b[27]	ESCC (risk)	Pooled analysis of hospital-based case-control studies	NA	5 case-control	NA	<u>Ex- *vs.* current drinkers</u> Men – OR=0.7 (0.5-0.9) <u>Never *vs.* current drinkers</u>

		conducted in high-risk areas in South America				Men – OR=0.3 (0.1-0.7) <u>Years since quitting drinking</u> *Men* 1-2 – OR=0.8 (0.6-1.3) 3-5 – OR=0.7 (0.4-1.2) 6-9 – OR=0.7 (0.3-1.2) 10-18 – OR=0.6 (0.3-1.1) ≥ 19 – OR=0.4 (0.2-0.8) <u>Trend per cessation year</u> Men – OR=0.96 (0.94-0.98)
Bagnardi, 2001[12]	EC (risk)	MEDLINE, Current Contents, EMBASE, CAB Abstracts and Core Biomedical Collection (1966-2000) Citation tracking	Not stated	28 1 cohort 27 case-control	No	<u>Dose-response analysis</u> *All studies* 25 g/day – RR=1.51 (1.48-1.55) 50 g/day – RR=2.21 (2.11-2.31) 100 g/day – RR=4.23 (3.91-4.59) *Studies presenting unadjusted estimates for smoking* 25 g/day – RR=1.50 (1.47-1.55) 50 g/day – RR=2.19 (2.08-2.31) 100 g/day – RR=4.18 (3.79-4.60) *Studies presenting adjusted estimates for smoking* 25 g/day – RR=1.52 (1.46-1.57) 50 g/day – RR=2.23 (2.09-2.38) 100 g/day – RR=4.31 (3.84-4.85) ACCORDING TO SEX *Men* 25 g/day – RR=1.43 (1.38-1.48) 50 g/day – RR=1.98 (1.87-2.11) 100 g/day – RR=3.49 (3.14-3.89) *Women* 25 g/day – RR=1.52 (1.42-1.63) 50 g/day – RR=2.24 (1.95-2.58) 100 g/day – RR=4.45 (3.37-5.87)
Zeka, 2003[23]	EC, ESCC, EAC (risk)	MEDLINE (1966-2001)	Not stated	8 case-control	No	<u>Trend estimation (*per* 100g/week of consumption)</u> *Esophageal cancer*

						β=0.14 (SE: 0.03), n=8, I^2=77% *Esophageal adenocarcinoma* β=0.05 (SE: 0.03), n=2, I^2=0% *Esophageal squamous cell carcinoma* β=0.18 (SE: 0.01), n=2, I^2=0% *Mixed esophageal carcinoma* β=0.19 (SE: 0.09), n=2, I^2=92%
Corrao, 2004[15]	EC (risk)	MEDLINE, EMBASE (1966-1998) Citation tracking	*The search process involved combining the keywords ''alcohol consumption'', ''relative risk'', and the specific ''conditions''. These keywords were exploded in the search, thus to include all the articles investigating the same issue, but reporting the same term in different forms (i.e., ''alcohol consumption'' or ''alcohol intake'', ''relative risk'' or ''risk ratio'' or ''odds ratio'', ''cancer'' or ''malignant neoplasm'' or ''neoplasia'', ''cerebrovascular disease'' or ''stroke'')* No language restrictions.	14 1 cohort 13 case-control	Questions related to the study design, alcohol consumption data collection methods and data analysis were used to obtain quality score.	<u>Dose-response analysis</u> *All studies* 25 g/day – RR=1.39 (1.36-1.42) 50 g/day – RR=1.93 (1.85-2.00) 100 g/day – RR=3.59 (3.34-3.87)
Ishikawa, 2006[17]	EC (incidence)	Pooled analysis of prospective cohort studies conducted in Miyagi Prefecture, Japan	NA	2 cohort	NA	<u>Former *vs.* never/occasionally drinkers</u> HR=1.55 (0.58-4.14) <u>Daily *vs.* never/occasionally drinkers</u> HR=2.73 (1.55-4.81)
Rehm, 2007[43]	EC (risk)	MEDLINE (1966-2006), EMBASE (1980-2006), WEB OF SCIENCE (1980-2006), PSYCHINFO (1980-2006) Citation tracking	*The following key search terms were used: (["mouth cancer" OR "oral cavity cancer" OR "oropharynx cancer" OR "oropharyngeal cancer OR "pharyngeal cancer" OR "head and neck cancer" OR "esophageal cancer"] AND "alcohol") AND ("risk" OR "association") AND ("cessation" OR "stopping drinking" OR "quitting drinking" OR "abstinence")* Restricted to studies published in English	5 case-control	No	<u>Years since cessation *vs.* current drinkers</u> *All studies* >0-2 – OR=2.50 (2.23-2.80) 2-5 – OR=1.10 (1.03-1.17) 5-10 – OR=0.85 (0.78-0.92) 10-15 – OR=0.85 (0.79-0.92) >15 – OR=0.37 (0.33-0.41) Never drinkers – OR=0.37 (0.35-0.39) *Studies presenting adjusted estimates for smoking* >0-2 – OR=2.50 (2.23-2.80) 2-5 – OR=1.10 (1.03-1.18) 5-10 – OR=0.85 (0.79-0.92) 10-15 – OR=0.85 (0.79-0.92)

						>15 – OR=0.35 (0.31-0.39) Never drinkers – OR=0.37 (0.35-0.39)
WCRF, 2007[22]	EC (risk, incidence, mortality)	MEDLINE, WEB OF SCIENCE, CINAHL, BIOSIS, CAB Abstracts, LILACS, EMBASE COCHRANE (inception-2006) Citation tracking	*Not specifically stated* No language restrictions	21 1 cohort 20 case-control	No	*Total alcoholic drinks* <u>Per 1 drink/week increment</u> Cohort – RR=1.26 (1.10-1.44), n=1 Case-control – RR=1.04 (1.03-1.05), n=20, I^2=90.6% *Beers* <u>Per 1 drink/week increment</u> RR=1.05 (1.03-1.07), n=5, I^2=90.5%
Rota, 2010[33]	ESCC (risk, incidence, mortality)	MEDLINE (inception-2008) Citation tracking	*Not stated*	15 1 cohort 14 case-control	No	<u>Ethanol in grams/day (reference category: 0)</u> 25 – OR=2.81 (1.79-4.40) 50 – OR=5.11 (2.63-9.94) 100 – OR=11.00 (4.61-26.24)
Freedman, 2011[29]	ESCC, EAC (risk)	International BEACON Consortium	NA	12 2 nested case-control 9 case-control	NA	*EAC* <u>Drinks/day (reference category: 0)</u> *All types* >0-0.5 – OR=0.86 (0.65-1.13), I^2=41% 0.5-<1 – OR=0.63 (0.41-0.99), I^2=63% 1-<3 – OR=0.81 (0.60-1.09), I^2=44% 3-<5 – OR=0.86 (0.59-1.24), I^2=47% 5-<7 – OR=0.93 (0.66-1.31), I^2=0% ≥7 – OR=0.97 (0.68-1.36), I^2=16% *Beer* >0-0.5 – OR=0.75 (0.53-1.07), I^2=51% 0.5-<1 – OR=0.71 (0.44-1.15), I^2=43% 1-<3 – OR=0.72 (0.51-1.04), I^2=8% 3-<5 – OR=0.60 (0.36-1.01), I^2=16% ≥5 – OR=0.63 (0.40-0.99), I^2=0% *Liquor* >0-0.5 – OR=0.71 (0.49-1.02), I^2=56% 0.5-<1 – OR=0.95 (0.66-1.35), I^2=4% 1-<3 – OR=1.09 (0.60-1.97), I^2=59% 3-<5 – OR=1.27 (0.75-2.13), I^2=0% ≥5 – OR=1.52 (0.82-2.80), I^2=0%

Wine
>0-0.5 – OR=0.67 (0.45-0.99), I^2=57%
0.5-<1 – OR=0.59 (0.39-0.88), I^2=11%
1-<3 – OR=0.71 (0.49-1.03), I^2=5%
≥3 – OR=1.49 (0.80-2.78), I^2=0%

Drinks/day (reference category: 0)
All types
>0-0.5 – OR=0.86 (0.65-1.13), I^2=41%
0.5-<1 – OR=0.63 (0.41-0.99), I^2=63%
1-<3 – OR=0.81 (0.60-1.09), I^2=44%
3-<5 – OR=0.86 (0.59-1.24), I^2=0%

ACCORDING TO SEX
Women
>0-0.5 – OR=1.20 (0.59-2.44), I^2=28%
0.5-<1 – OR=0.85 (0.35-2.09), I^2=0%
1-<3 – OR=1.29 (0.63-2.67), I^2=0%
3-<5 – OR=4.25 (1.60-11.30), I^2=0%

Men
>0-0.5 – OR=0.77 (0.55-1.08), I^2=48%
0.5-<1 – OR=0.58 (0.35-0.95), I^2=65%
1-<3 – OR=0.74 (0.50-1.07), I^2=57%
3-<5 – OR=0.74 (0.48-1.15), I^2=54%
≥5 – OR=0.85 (0.65-1.11), I^2=0%

ACCORDING TO GERD
No reflux
>0-0.5 – OR=0.69 (0.43-1.10), I^2=20%
0.5-<1 – OR=0.48 (0.30-0.77), I^2=0%
1-<3 – OR=0.55 (0.33-0.92), I^2=37%
3-<5 – OR=0.49 (0.31-0.80), I^2=0%
≥5 – OR=0.55 (0.34-0.89), I^2=0%

Reflux
>0-0.5 – OR=0.87 (0.52-1.47), I^2=28%
0.5-<1 – OR=0.44 (0.24-0.81), I^2=30%
1-<3 – OR=0.80 (0.53-1.22), I^2=0%
3-<5 – OR=0.66 (0.39-1.10), I^2=0%
≥5 – OR=1.21 (0.74-1.99), I^2=0%

ACCORDING TO SMOKING

Never smokers
>0-0.5 – OR=0.96 (0.68-1.35), I^2=0%
0.5-<1 – OR=0.67 (0.41-1.08), I^2=0%
1-<3 – OR=0.82 (0.54-1.24), I^2=0%
3-<5 – OR=0.71 (0.38-1.34), I^2=0%
≥5 – OR=1.38 (0.71-2.69), I^2=0%

Former smokers
>0-0.5 – OR=0.66 (0.38-1.15), I^2=58%
0.5-<1 – OR=0.62 (0.29-1.31), I^2=73%
1-<3 – OR=0.73 (0.41-1.29), I^2=65%
3-<5 – OR=0.84 (0.47-1.50), I^2=52%
≥5 – OR=0.85 (0.57-1.27), I^2=1%

Current smokers
>0-0.5 – OR=1.01 (0.58-1.75), I^2=0%
0.5-<1 – OR=0.67 (0.33-1.38), I^2=0%
1-<3 – OR=0.78 (0.43-1.44), I^2=0%
3-<5 – OR=0.85 (0.44-1.63), I^2=0%
≥5 – OR=1.09 (0.61-1.97), I^2=0%

ACCORDING TO BMI
18.5-<25 Kg/m^2
>0-0.5 – OR=0.90 (0.61-1.32), I^2=0%
0.5-<1 – OR=0.63 (0.30-1.34), I^2=51%
1-<3 – OR=1.00 (0.63-1.59), I^2=25%
3-<5 – OR=0.99 (0.59-1.64), I^2=6%
≥5 – OR=1.19 (0.74-1.92), I^2=0%

25-<30 Kg/m^2
>0-0.5 – OR=0.75 (0.50-1.13), I^2=31%
0.5-<1 – OR=0.58 (0.35-0.97), I^2=40%
1-<3 – OR=0.68 (0.43-1.07), I^2=42%
3-<5 – OR=0.79 (0.48-1.31), I^2=35%
≥5 – OR=0.69 (0.46-1.03), I^2=0%

30-<35 Kg/m^2
>0-0.5 – OR=1.09 (0.63-1.90), I^2=0%
0.5-<1 – OR=1.00 (0.30-3.28), I^2=45%
1-<3 – OR=0.65 (0.33-1.25), I^2=0%
3-<5 – OR=0.63 (0.12-3.26), I^2=66%
≥5 – OR=0.54 (0.24-1.22), I^2=0%

						≥35 Kg/m² >0-0.5 – OR=2.43 (0.74-7.96), I^2=0% 0.5-<1 – OR=1.23 (0.22-6.89), I^2=0% 1-<3 – OR=1.79 (0.35-9.24), I^2=0% 3-<5 – OR=0.99 (0.14-6.88), I^2=0% ≥5 – OR=3.61 (0.76-17.04), I^2=0% <u>Duration in years (reference category: 0)</u> >0-<10 – OR=0.94 (0.56-1.57), I^2=0% 10-<20 – OR=1.15 (0.77-1.74), I^2=1% 20-<30 – OR=0.83 (0.55-1.24), I^2=24% 30-<40 – OR=0.76 (0.53-1.07), I^2=17% 40-<50 – OR=0.74 (0.49-1.10), I^2=37% ≥50 – OR=0.71 (0.48-1.05), I^2=22% <u>Drinks-years (reference category: 0)</u> >0-<25 – OR=0.75 (0.56-0.99), I^2=0% 25-<50 – OR=0.66 (0.44-0.99), I^2=26% 50-<100 – OR=0.75 (0.54-1.02), I^2=0% 100-<200 – OR=0.67 (0.48-0.94), I^2=0% 200-<300 – OR=1.04 (0.69-1.57), I^2=0% ≥300 – OR=0.97 (0.50-1.88), I^2=45% *ESCC* <u>Drinks/day (reference category: 0)</u> *All types* >0-0.5 – OR=0.80 (0.56-1.14), I^2=18% 0.5-<1 – OR=1.23 (0.55-2.74), I^2=67% 1-<3 – OR=2.56 (1.10-5.96), I^2=79% 3-<5 – OR=4.56 (2.32-8.96), I^2=67% 5-<7 – OR=7.17 (2.98-17.25), I^2=69% ≥7 – OR=9.62 (4.26-21.71), I^2=71%
Islami, 2011[30]	ESCC (risk)	Previous meta-analysis plus MEDLINE (1999-2010) Citation tracking	*''Esophageal Neoplasms'' [MeSH Terms] and [cohort OR prospective OR (case-control) OR (case control)]*	53 13 cohort 40 case-control	No	<u>Light intake (< 12.5 g/day)</u> All studies – RR=1.31 (1.10-1.57), n=26, I^2=56.2% Cohort – RR=1.35 (0.92-1.98), n=8, I^2=81.1% More precise estimates – RR=1.32 (0.90-1.60), n=19, I^2=73.2% Population-based controls – RR=1.16 (0.87-1.55), n=13, I^2=77.3% Only ESCC – RR=1.25 (1.01-1.56), n=16, I^2=61.0%

Adjusted results – RR=1.38 (1.14-1.67), n=19, I^2=51.5%

ACCORDING TO GEOGRAPHIC AREA
All studies
Asia – RR=1.63 (1.20-2.22), n=9, I^2=73.1%
Other regions – RR=1.17 (0.99-1.39), n=17, I^2=32.8%
Adjusted results (at least for age, alcohol and tobacco)
Asia – RR=1.52 (1.06-2.19), n=8, I^2=67.4%
Other regions – RR=1.28 (1.04-1.59), n=11, I^2=32.1%
Prospective studies
Asia – RR=1.89 (1.49-2.41), n=5, I^2=17.8%
Other regions – RR=1.03 (0.76-1.39), n=3, I^2=29.2%

Moderate intake (12.5-50 g/day)
All studies – RR=2.27 (1.89-2.72), n=47, I^2=85.3%
Cohort – RR=2.15 (1.55-2.98), n=12, I^2=86.7%
More precise estimates – RR=2.23 (1.84-2.71), n=38, I^2=87.1%
Population-based controls – RR=1.92 (1.49-2.47), n=23, I^2=85.0%
Only ESCC – RR=2.32 (1.80-2.99), n=27, I^2=85.8%
Adjusted results – RR=2.62 (2.07-3.31), n=28, I^2=82.8%

ACCORDING TO GEOGRAPHIC AREA
All studies
Asia – RR=2.17 (1.58-2.96), n=21, I^2=90.9%
Other regions – RR=2.34 (1.90-2.88), n=26, I^2=74.1%
Adjusted results (at least for age, alcohol and tobacco)
Asia – RR=2.52 (1.69-3.74), n=14, I^2=88.4%
Other regions – RR=2.69 (2.05-3.53), n=14, I^2=71.3%
Prospective studies
Asia – RR=1.96 (1.20-3.22), n=8, I^2=88.8%
Other regions – RR=2.46 (1.55-3.90), n=4, I^2=82.7%

High intake (> 50 g/day)
All studies – RR=4.89 (3.84-6.23), n=39, I^2=87.1%
Cohort – RR=3.35 (2.06-5.46), n=9, I^2=91.4%

						More precise estimates – RR=3.35 (2.35-4.78), n=16, I^2=94.5% Population-based controls – RR=3.77 (2.60-5.47), n=18, I^2=91.0% Only ESCC – RR=5.38 (3.80-7.61), n=20, I^2=88.4% Adjusted results – RR=5.54 (3.92-7.82), n=21, I^2=89.9% ACCORDING TO GEOGRAPHIC AREA *All studies* Asia – RR=4.02 (2.76-5.83), n=18, I^2=91.6% Other regions – RR=5.73 (4.41-7.44), n=21, I^2=79.9% *Adjusted results (at least for age, alcohol and tobacco)* Asia – RR=4.31 (2.46-7.55), n=10, I^2=91.8% Other regions – RR=6.94 (4.71-10.22), n=11, I^2=83.3% *Prospective studies* Asia – RR=3.65 (2.03-6.55), n=7, I^2=92.3% Other regions – RR=2.64 (0.75-9.37), n=2, I^2=93.3%
Li, 2011[19]	EC (risk, incidence, mortality)	MEDLINE, EMBASE, CNKI, VIP (inception-2010) Citation tracking	*mixture of free text and index terms* Restricted to studies conducted on Chinese populations and published in English or Chinese.	36 2 cohort 34 case-control	Newcastle-Ottawa scale	Drinkers *vs.* non drinkers All studies – RR=1.78 (1.38-2.30), n=36, I^2=90% ACCORDING TO SEX Men – RR=1.82 (1.49-2.22) Women – RR=0.91 (0.47-1.77) ACCORDING TO STUDY DESIGN Cohort – RR=1.08 (0.94-1.23), n=2, I^2=96% Case-control – RR=1.79 (1.47-2.17), n=34, I^2=87%
Oze, 2011[20]	EC (risk)	MEDLINE (1950-2010), Ichushi (1983-2010) Citation tracking	*using the following as keywords: alcohol, esophagus, esophageal cancer, cohort, follow-up, case–control, Japan and Japanese* Restricted to studies conducted on Japanese populations and published in English or Japanese.	13 4 cohort 9 case-control	No	Ever *vs.* never drinkers All studies – RR=3.30 (2.30-4.74), n=12, I^2=80%, Egger test: p=0.713 Only adjusted estimates for smoking – RR=3.36 (1.66-6.78), n=4, I^2=83%
Jarl, 2012[42]	EC (risk)	MEDLINE (inception-2011), Google Scholar (first 30 hits) Citation tracking	*['alcohol' AND ('oesophageal cancer' OR 'esophageal cancer') AND 'risk' AND ('cessation' OR 'quit drinking' OR 'quitting drinking' OR 'stop drinking' OR 'stopping drinking' OR 'abstainers' OR 'abstinence')]* Restricted to studies published in English	17 2 cohort 15 case-control	No	Alcohol cessation (high *vs.* current) OR=0.46 (0.34-0.63), n=9, I^2=26.6%

Lubin, 2012[31]	ESCC, EAC (risk)	International BEACON Consortium	NA	12 2 nested case-control 10 case-control	NA	<u>Drink-years (reference category: 0)</u> *Esophageal adenocarcinoma* 1-49 – OR=0.74 (0.6-0.9) 50-99 – OR=0.77 (0.5-1.1) 100-149 – OR=0.60 (0.4-0.9) 150-199 – OR=0.62 (0.4-1.1) ≥200 – OR=0.67 (0.4-1.2) *Esophageal squamous cell carcinoma* 1-49 – OR=1.31 (0.9-1.9) 50-99 – OR=2.18 (1.3-3.8) 100-149 – OR=2.96 (1.6-5.3) 150-199 – OR=3.52 (1.8-6.9) ≥200 – OR=3.82 (1.9-7.8) <u>Drinks/day (reference category: 0.1-1.0)</u> *Esophageal adenocarcinoma* 1.0-2.9 – OR=1.09 (0.8-1.4) 3.0-4.9 – OR=1.27 (0.8-1.9) 5.0 -9.9– OR=1.56 (0.9-2.7) ≥10 – OR=1.87 (0.9-3.7) *Esophageal squamous cell carcinoma* 1.0-2.9 – OR=1.32 (0.9-1.9) 3.0-4.9 – OR=2.15 (1.3-3.6) 5.0 -9.9– OR=2.74 (1.5-5.2) ≥10 – OR=4.12 (2.0-8.4)
Tramacere, 2012[35]	EAC (risk)	MEDLINE (inception-2010) Citation tracking	*MeSH terms 'alcohol drinking' or 'alcoholic beverages' and 'stomach neoplasms' or 'esophageal neoplasms'* Restricted to studies published in English	24 4 cohort 20 case–control	No	<u>Drinkers *vs.* non drinkers</u> RR=0.87 (0.74-1.01), n=13, I^2=35.7% <u>Heavy alcohol drinkers (≥ 4 drinks per day) *vs.* non drinkers</u> RR=1.10 (0.80-1.50), n=7
Bagnardi, 2013[24]	ESCC (risk)	MEDLINE, WEB OF SCIENCE, EMBASE (inception-2010) Citation tracking	*((ethanol) OR (alcohol drinking)) AND lip neoplasm OR tongue neoplasm OR salivary gland neoplasm OR gingival neoplasm OR mouth neoplasm OR pharynx neoplasm OR Laryngeal neoplasm OR esophageal neoplasm OR Intestinal neoplasm OR Colorectal neoplasm OR Breast neoplasm OR liver neoplasm*	27 9 cohort 18 case-control	No	<u>Light drinking</u> All studies – RR=1.30 (1.09-1.56), n=27, I^2=67% ACCORDING TO SEX Men – RR=1.46 (1.19-1.80), n=14 Women – RR=1.28 (0.84-1.96), n=5

			Restricted to studies published in English			ACCORDING TO STUDY DESIGN Cohort – RR=1.34 (0.96-1.87), n=9 Case-control – RR=1.28 (1.04-1.59), n=18 ACCORDING TO GEOGRAPHIC AREA Europe – RR=1.05 (0.79-1.38), n=7 North America – RR=1.21 (0.96-1.54), n=8 Asia – RR=1.49 (1.12-1.98), n=10
Prabhu, 2013[32]	ESCC (risk)	MEDLINE (1948-2013), EBM reviews (inception-2013), EMBASE (1947-2011), ISI Web of Knowledge (inception-2013), BIOSIS preview (1926-2013)	*Key index terms for our literature review included {esophageal carcinoma, esophageal neoplasm or [esophagus and (squamous cell carcinoma, carcinoma, cancer, neoplasms, adenosquamous carcinoma or basosquamous carcinoma)]} and (risk factors, tobacco, tobacco smokeless, tobacco use disorder, tobacco smoke pollution, smoke, smoking, marijuana smoking, cigarette, cigar, alcohols, alcohol, alcohol drinking, alcoholism, alcohol abuse, ethanol, alcoholic beverages, liquor, beer, wine, spirits, or alcoholic intoxication), also using the alternative spelling 'oesophageal' or 'oesophagus'* No language restrictions	18 5 cohort 13 case-control	Newcastle-Ottawa Scale 6 highest quality studies	<u>≥200 g of alcohol/week *vs.* never drinkers</u> All studies – OR=4.65 (3.61-5.99), n=18, I^2=71% Only highest quality studies – OR=3.49 (2.82-4.32), n=6, I^2=37% ACCORDING TO STUDY DESIGN Cohort – OR=3.51 (3.09-4.00), n=5, I^2=0% Case-control – OR=5.20 (3.30-8.18), n=13, I^2=80% ACCORDING TO RACE/CONTINENT Asia – OR=5.80 (3.64-9.24), n=8, I^2=77% (East Asia – OR=6.15 (3.80-9.96), n=7, I^2=77%) Europe – OR=3.87 (2.57-5.82), n=8, I^2=56% (Southern Europe – OR=5.93 (3.18-11.06), n=4, I^2=40%) (Northern Europe – OR=2.92 (1.88-4.53), n=4, I^2=43%) <u><200 g of alcohol/week *vs.* never drinkers</u> All studies – OR=1.71 (1.22-2.42), n=18, I^2=89%
Li, 2014[18]	EC (mortality)	MEDLINE (inception-2013), ISI Web of Knowledge (inception-2013) Citation tracking	*(alcohol OR alcoholic beverages) AND cancer AND mortality AND (prospective OR cohort OR case-control OR case-cohort)* No language restrictions	10 8 cohort 1 nested case-control 1 case-control	Jin *et al.*, 2013	<u>Drinking *vs.* non/occasional</u> RR/OR=1.86 (1.40-2.47), n=8, I^2=72.2% <u>Light drinking (≤12.5 g/day) *vs.* non/occasional</u> RR/OR=1.43 (1.09-1.87), n=5, I^2=61.0% <u>Moderate drinking (12.5-50 g/day) *vs.* non/occasional</u> RR/OR=1.92 (1.25-2.96), n=7, I^2=81.2% <u>Heavy drinking (≥50 g/day) *vs.* non/occasional</u> RR/OR=3.37 (2.30-4.93), n=8, I^2=71.1% No evidence of publication bias

Bagnardi, 2015[25]	ESCC (risk)	MEDLINE (inception-2012), ISI Web of Knowledge (inception-2012), EMBASE (inception-2012) Citation tracking	*MeSH terms search* *1. ethanol* *2. alcohol drinking* *3. lip neoplasms OR tongue neoplasms OR salivary gland neoplasms OR gingival neoplasms OR mouth neoplasms OR pharyngeal neoplasms OR esophageal neoplasms OR intestinal neoplasms OR stomach neoplasms OR colorectal neoplasms OR liver neoplasms OR gallbladder neoplasms OR pancreatic neoplasms OR laryngeal neoplasms OR lung neoplasms OR carcinoma, basal cell OR melanoma OR carcinoma, squamous cell OR breast neoplasms OR uterine cervical neoplasms OR endometrial neoplasms OR ovarian neoplasms OR prostatic neoplasms OR kidney neoplasms OR renal cell carcinoma OR urinary bladder neoplasms OR thyroid neoplasms OR brain neoplasms OR Non-Hodgkin lymphoma OR Hodgkin disease OR neoplasms* *4. ((1) OR (2)) AND 3* *Direct keyword search* *5. alcohol* *6. alcoholic beverages* *7. (1)* *8. (2)* *9. (3)* *10. lip cancer OR tongue cancer OR salivary gland cancer OR gingival cancer OR mouth cancer OR pharyngeal cancer OR esophageal cancer OR intestinal cancer OR stomach cancer OR colorectal cancer OR liver cancer OR gallbladder cancer OR pancreatic cancer OR laryngeal cancer OR lung cancer OR skin cancer OR basal cell carcinoma OR squamous cell carcinoma OR melanoma OR breast cancer OR uterine cervical cancer OR endometrial cancer OR ovarian cancer OR prostatic cancer OR kidney cancer OR renal cell carcinoma OR urinary bladder cancer OR thyroid cancer OR brain cancer OR Non-Hodgkin lymphoma OR Hodgkin disease OR cancer* *11. ((5) OR (6) OR (7) OR (8)) AND ((9) OR (10))* *12. (4) OR (11)* No language restrictions	54 13 cohort 41 case-control	No	<u>Light drinking *vs.* non and occasional drinkers</u> All studies – RR=1.26 (1.06-1.50), n=34, I^2=68% Adjusted estimates only – RR=1.34 (1.12-1.58) Estimates that did not consider occasional drinkers in the reference category – RR=1.30 (1.08-1.55) ACCORDING TO STUDY DESIGN Cohort – RR=1.20 (0.84-1.71), n=10, I^2=84% Case-control – RR=1.29 (1.07-1.55), n=24, I^2=49% ACCORDING TO SEX Men – RR=1.39 (1.11-1.74), n=16, I^2=61% Women – RR=1.14 (0.87-1.49), n=8, I^2=43% ACCORDING TO POPULATION GROUP European – RR=1.05 (0.79-1.38), n=7, I^2=22% North American – RR=1.07 (0.84-1.37), n=12, I^2=32% Asian – RR=1.54 (1.18-2.00), n=11, I^2=71% <u>Moderate drinking *vs.* non and occasional drinkers</u> RR=2.23 (1.87-2.65), n=53, I^2=85% Adjusted estimates only – RR=2.56 (2.05-3.20) Estimates that did not consider occasional drinkers in the reference category – RR=2.16 (1.72-2.71) ACCORDING TO STUDY DESIGN Cohort – RR=1.92 (1.44-2.58), n=13, I^2=83% Case-control – RR=2.34 (1.87-2.92), n=40, I^2=86% ACCORDING TO SEX Men – RR=2.25 (1.78-2.85), n=28, I^2=85% Women – RR=2.18 (1.42-3.35), n=8, I^2=72% ACCORDING TO POPULATION GROUP European – RR=1.91 (1.32-2.77), n=10, I^2=71% North American – RR=2.95 (2.38-3.67), n=13, I^2=37% Asian – RR=2.20 (1.65-2.94), n=23, I^2=91% <u>Heavy drinking *vs.* non and occasional drinkers</u> RR=4.95 (3.86-6.34), n=41, I^2=91% Adjusted estimates only – RR=5.45 (3.80-7.83)

							Estimates that did not consider occasional drinkers in the reference category – RR=4.53 (3.39-6.05) ACCORDING TO STUDY DESIGN Cohort – RR=3.56 (2.25-5.64), n=9, I^2=91% Case-control – RR=5.43 (4.04-7.32), n=32, I^2=91% ACCORDING TO SEX Men – RR=4.69 (3.49-6.31), n=24, I^2=88% Women – RR=8.32 (2.95-23.45), n=3, I^2=72% ACCORDING TO POPULATION GROUP European – RR=4.76 (2.69-8.41), n=8, I^2=85% North American – RR=7.63 (5.34-10.91), n=10, I^2=59% Asian – RR=4.24 (2.93-6.14), n=18, I^2=93%
Drahos, 2015[34]	EAC (risk)	International BEACON Consortium	NA		8 case-control	NA	<u>Ever *vs.* never drinkers</u> All age groups – OR=0.78 (0.64-0.96) ACCORDING TO AGE GROUP < 50 years – OR=0.95 (0.42-2.13) 50-59 years – OR=0.73 (0.45-1.17) 60-69 years – OR=1.00 (0.70-1.42) ≥ 70 years – OR=0.62 (0.45-0.85) <u>> 0 - < 0.5 drinks per day *vs.* none</u> All age groups – OR=0.78 (0.62-0.98) ACCORDING TO AGE GROUP < 50 years – OR=1.05 (0.43-2.58) 50-59 years – OR=0.72 (0.42-1.24) 60-69 years – OR=0.99 (0.66-1.48) ≥ 70 years – OR=0.63 (0.43-0.92) <u>0.5 - < 1.0 drinks per day *vs.* none</u> All age groups – OR=0.55 (0.42-0.72) ACCORDING TO AGE GROUP < 50 years – OR=0.44 (0.14-1.36) 50-59 years – OR=0.47 (0.25-0.88) 60-69 years – OR=0.72 (0.45-1.13) ≥ 70 years – OR=0.53 (0.34-0.82)

						<u>1 - <3 drinks per day *vs.* none</u> All age groups – OR=0.74 (0.58-0.93) ACCORDING TO AGE GROUP < 50 years – OR=0.85 (0.35-2.07) 50-59 years – OR=0.71 (0.42-1.20) 60-69 years – OR=0.84 (0.56-1.26) ≥ 70 years – OR=0.66 (0.45-0.96) <u>3 - <5 drinks per day *vs.* none</u> All age groups – OR=0.69 (0.52-0.91) ACCORDING TO AGE GROUP < 50 years – OR=0.93 (0.34-2.53) 50-59 years – OR=0.51 (0.27-0.94) 60-69 years – OR=0.90 (0.56-1.45) ≥ 70 years – OR=0.55 (0.33-0.89) <u>≥ 7 drinks per day *vs.* none</u> All age groups – OR=0.93 (0.66-1.30) ACCORDING TO AGE GROUP < 50 years – OR=1.55 (0.47-5.10) 50-59 years – OR=0.85 (0.41-1.74) 60-69 years – OR=1.34 (0.76-2.36) ≥ 70 years – OR=0.48 (0.24-0.97)
Fahey, 2015[28]	ESCC, EAC (mortality)	MEDLINE (inception-2014), EMBASE (inception-2014) Citation tracking	("Esophagus"[Mesh] OR "Esophagus"[Title/Abstract] OR "Oesophagus"[Title/Abstract] OR "Esophageal"[Title/Abstract] OR "Oesophageal"[Title/Abstract]) AND ("Neoplasms"[Mesh] OR "Neoplasm"[Title/Abstract] OR "Cancer*"[Title/Abstract] OR "Carcinoma"[Title/Abstract] OR "Adenocarcinoma"[Title/Abstract]) AND (("Survival" [Mesh]) OR ("Prognosis" [Mesh]) OR ("survival" [Title/Abstract]) OR ("prognosis" [Title/Abstract]) OR ("prognostic" [Title/Abstract])) AND (("smoking" [Title/Abstract]) OR ("tobacco" [Title/Abstract]) OR ("alcohol" [Title/Abstract]) OR ("physical activity" [Title/Abstract]) OR ("exercise" [Title/Abstract]) OR ("sedentary lifestyle"[Title/Abstract]) OR ("body mass index"[Title/Abstract]) OR ("BMI" [Title/Abstract]) OR ("obesity" [Title/Abstract]) OR ("Aspirin"[Title/Abstract]) OR ("Non-Steroidal Anti-Inflammatory"[Title/Abstract]) OR	9	JAMA	<u>Ever *vs.* never drinkers</u> *ESCC* HR=1.36 (1.15-1.61), n=6, I^2=67.9% *EAC* HR=1.08 (0.85-1.37), n=2, I^2=0.0% <u>Highest *vs.* lowest alcohol consumption category</u> *ESCC* HR=1.40 (1.07-1.82), n=4, I^2=54.0% *EAC* HR=0.97 (0.73-1.30), n=2, I^2=0.0%

			("NSAID"[Title/Abstract]) OR ("health behavior"[Title/Abstract]) OR ("health behaviour"[Title/Abstract]) OR ("life style"[Title/Abstract]) OR ("lifestyle"[Title/Abstract]) OR ("life-style"[Title/Abstract]) OR ("Smoking"[Mesh]) OR ("Alcohol Drinking"[Mesh]) OR ("Motor Activity"[Mesh]) OR ("Exercise"[Mesh]) OR ("Sedentary Lifestyle"[Mesh]) OR ("Body Mass Index"[Mesh]) OR ("Obesity"[Mesh]) OR ("Health Behavior"[Mesh]) OR ("Life Style"[Mesh]) OR ("Aspirin"[Mesh]) OR ("Anti-Inflammatory Agents, Non-Steroidal"[Mesh])) Restricted to studies published in English			No evidence of publication bias
Roerecke, 2015[21]	EC (risk)	IARC monographs (2010, 2012), MEDLINE (inception-2014) Citation tracking	*"alcohol or ethanol" and "cohort" and "cancer" and "japan" and "review" and "mortality"* Restricted to studies conducted in Japan after 1980	7 3 cohort 4 case-control	No	<u>Per 100 g/day of pure alcohol intake</u> Cohort – RR=11.71 (2.67-51.32), n=3, I^2=60% Case-control – RR=33.11 (8.15-134.43), n=4, I^2=89%
SMOKING						
Castellsagué, 1999[26]	ESCC (risk)	Pooled analysis of hospital-based case-control studies conducted in high-risk areas in South America	NA	5 case-control	NA	<u>Ever *vs.* never smokers</u> Men – OR=4.1 (2.7-6.0) Women – OR=2.4 (1.5-3.7) <u>Current *vs.* never smokers</u> Men – OR=5.1 (3.4-7.6) Women – OR=3.1 (1.8-5.3) <u>Ex- *vs.* never smokers</u> Men – OR=2.8 (1.8-4.3) Women – OR=1.6 (0.8-3.1) <u>Average number of cigarettes/day</u> *Men* 1-7 – OR=2.2 (1.3-3.5) 8-14 – OR=4.1 (2.6-6.4) 15-24 – OR=5.3 (3.4-8.1) ≥ 25 – OR=5.0 (3.2-7.7) *Women* 1-14 – OR=2.1 (1.2-3.7) ≥ 15 – OR=2.8 (1.4-5.4)

			Years of cigarette smoking *Men* 1-29 – OR=2.6 (1.7-4.2) 30-39 – OR=3.6 (2.3-5.6) 40-49 – OR=4.7 (3.0-7.2) ≥ 50 – OR=6.0 (3.8-9.5) *Women* 1-29 – OR=1.5 (0.8-2.9) 30-39 – OR=2.0 (0.9-4.4) ≥ 40 – OR=4.4 (2.2-9.0) Age at starting smoking *Men* 14-16 – OR=0.7 (0.5-0.96) 17-20 – OR=0.8 (0.6-1.0) ≥ 21 – OR=0.6 (0.4-0.9) *Women* 14-16 – OR=1.6 (0.3-7.5) 17-20 – OR=0.6 (0.2-2.4) ≥ 21 – OR=0.2 (0.1-0.7) Age at quitting smoking *Men* 44-53 – OR=0.8 (0.5-1.3) 54-62 – OR=1.0 (0.6-1.7) ≥ 63 – OR=1.5 (0.9-2.7) *Women* ≥ 54 – OR=7.6 (0.7-84.2) Years since quitting smoking *Men* 1-4 – OR=0.7 (0.5-1.0) 5-9 – OR=0.5 (0.3-0.8) ≥ 10 – OR=0.5 (0.4-0.7) *Women* 1-9 – OR=1.0 (0.3-3.1) ≥ 10 – OR=0.4 (0.1-1.2) Type of tobacco *Men* Mixed – OR=1.3 (0.8-1.9) Black only – OR=2.0 (1.5-2.7) *Women*

						Black only – OR=3.4 (0.9-13.0) <u>Use of filter</u> *Men* Ever – OR=0.8 (0.6-0.98) *Women* Ever – OR=1.5 (0.5-4.4)
Castellsagué, 2000b[27]	ESCC (risk)	Pooled analysis of hospital-based case-control studies conducted in high-risk areas in South America	NA	5 case-control	NA	<u>Ex- *vs.* current smokers</u> Men – OR=0.5 (0.4-0.7) <u>Never *vs.* current smokers</u> Men – OR=0.2 (0.1-0.4) <u>Years since quitting smoking</u> *Men* 1-2 – OR=0.7 (0.4-1.0) 3-7 – OR=0.6 (0.4-1.0) 8-12 – OR=0.4 (0.3-0.6) 13-23 – OR=0.5 (0.4-0.8) ≥ 24 – OR=0.5 (0.3-0.7) <u>Trend *per* cessation year</u> Men – OR=0.98 (0.97-0.99)
Zeka, 2003[23]	EC, ESCC, EAC (risk)	MEDLINE (1966-2001)	Not stated	8 case-control	No	<u>Trend estimation (*per* 100g/week of consumption)</u> *Esophageal cancer* β=0.28 (SE: 0.07), n=8, I^2=50% *Esophageal adenocarcinoma* β=0.24 (SE: 0.07), n=2, I^2=0% *Esophageal squamous cell carcinoma* β=0.22 (SE: 0.04), n=2, I^2=0% *Mixed esophageal carcinoma* β=0.33 (SE: 0.07), n=4, I^2=74%
Ishikawa, 2006[17]	EC (incidence)	Pooled analysis of prospective cohort studies conducted in Miyagi Prefecture, Japan	NA	2 cohort	NA	<u>Former *vs.* never smokers</u> HR=2.07 (0.66-6.57) <u>Current (1-19 cigarettes/day) *vs.* never smokers</u> HR=5.00 (1.70-14.66) <u>Current (≥20 cigarettes/day) *vs.* never smokers</u>

						HR=5.09 (1.80-14.40)
Gandini, 2008[39]	EC (risk)	Not stated	Not stated	22 5 cohort 17 case-control	Not stated	Current *vs.* never smokers RR=2.50 (2.00-3.13), n=22, I^2=81%, no evidence of publication bias ACCORDING TO SEX Men – RR=2.52 (1.81-3.52), n=7 Women – RR=2.28 (1.51-3.44), n=14 ACCORDING TO STUDY DESIGN Cohort – RR=2.30 (1.34-3.95), n=5 Case-control – RR=2.55 (1.94-3.36), n=17 ACCORDING TO ETHNIC GROUP African-Americans – RR=3.49 (1.49-8.20), n=1 Asians – RR=1.62 (1.14-2.31), n=6 Caucasians – RR=3.35 (1.89-5.92), n=5 ACCORDING TO GEOGRAPHIC AREA Western countries – RR=3.05 (2.23-4.17), n=11 Not Western countries – RR=2.08 (1.52-2.83), n=11 ACCORDING TO ADJUSTMENT FOR ALCOHOL INTAKE Adjusted – RR=3.00 (2.18-4.12), n=11 Not adjusted – RR=2.10 (1.52-2.88), n=11 Former *vs.* never smokers RR=2.03 (1.77-2.33), n=21, I^2=20%
Ansary-Moghaddam, 2009a[36]	EC (risk)	MEDLINE, EMBASE Citation tracking	*MeSH terms (all exploded): "esophageal", "laryngeal", "pharyngeal", or "oral cavity" together with "neoplasm", "squamous cell", "adenocarcinoma", or "cancer" together with "cohort study" or "case-control study"*	Not specified for EC	No	*After correction for publication bias* Current *vs.* never smokers RR=2.52 (2.14-2.95) Dose-response analysis <20 cigarettes/day – RR=2.36 (1.66-3.37) ≥20 cigarettes/day – RR=2.97 (2.01-4.40)
Ansary-Moghaddam, 2009b[37]	EC (mortality)	Asia Pacific Cohort Studies Collaboration	NA	26	NA	<20 cigarettes/day *vs.* never smokers HR=2.52 (1.25-5.07) ≥20 cigarettes/day *vs.* never smokers HR=3.40 (1.71-6.76)

						Ex- *vs.* current smokers HR=1.03 (0.66-1.63) Current *vs*. never smokers (adjusted for age and alcohol) HR=2.84 (1.72-4.68)
Akl, 2010[44]	EC (risk)	MEDLINE (1950-2008), EMBASE (1988-2008), WEB OF SCIENCE (inception-2008) Citation tracking	MEDLINE: *Waterpipe_.mp., ''water pipe_''.mp., shisha_.mp., sheesha_.mp., hooka_.mp., huqqa_.mp., guza_.mp., goza_.mp., narghil_.mp., nargil_.mp., arghil_.mp, argil_.mp, (hubbl_ adj3 bubbl_).mp., or/1–13* EMBASE: *Waterpipe_.mp., ''water pipe_''.mp., shisha_.mp., sheesha_.mp., hooka_.mp., huqqa_.mp., guza_.mp., goza_.mp., narghil_.mp., nargil_.mp., arghil_.mp, argil_.mp, (hubbl_ adj3 bubbl_).mp., or/1-13* WEB OF SCIENCE: *(waterpipe_ OR ''water pipe_'' OR shisha_ OR sheesha_ OR hooka_ OR huqqa_ OR guza_ OR goza_ OR narghil_ OR nargil_ OR argil_ OR arghil_ OR (hubbl_ SAME bubbl_)) AND (smoking OR smoke OR health OR disease OR cancer_ OR malignan_ OR lung_ OR pulmonary OR heart OR cardiac OR vascular OR stroke) (in Title or Topic)*	1 case-control for EC as outcome	GRADE	Waterpipe tobacco smoking *vs.* no smoking OR=1.85 (0.95-3.58), n=1
Cook, 2010[38]	EAC (risk)	International BEACON Consortium	NA	12 2 cohort 10 case-control	NA	*Analyses restricted to white non-Hispanic men and women* Ever *vs.* never smokers OR=1.96 (1.64-2.34), I^2=24% ACCORDING TO SEX Men – OR=2.10 (1.71-2.59) Women – OR=1.74 (1.21-2.51) Pack-years of smoking *vs.* never smokers <15 – OR=1.25 (1.02-1.53), I^2=0% 15-30 – OR=1.96 (1.58-2.45), I^2=0% 30-45 – OR=2.07 (1.66-2.58), I^2=2% ≥45 – OR=2.71 (2.16-3.40), I^2=24%
Tramacere, 2011[41]	EAC (risk)	MEDLINE (inception-2010) Citation tracking	*MESH terms "smoking" and combinations of "esophageal neoplasms" or "stomach neoplasms" and "adenocarcinoma"* Restricted to studies published in English	15 2 cohort 13 case-control	No	Ever *vs.* never smokers All studies – RR=1.85 (1.59-2.15), n=15, I^2=29.4% Cohort – RR=2.67 (1.94-3.67), n=2, I^2=0% Case-control – RR=1.71 (1.50-1.95), n=13, I^2=4.6%

Lubin, 2012[31]	ESCC, EAC (risk)	International BEACON Consortium	NA	12 2 nested case-control 10 case-control	NA	<u>Pack-years of smoking (reference category: 0)</u> *Esophageal adenocarcinoma* 1-29 – OR=1.66 (1.1-2.4) 30-39 – OR=1.45 (0.8-2.5) 40-49 – OR=2.22 (1.2-4.0) 50-59 – OR=1.92 (1.0-3.6) ≥60 – OR=2.77 (1.4-5.6) *Esophageal squamous cell carcinoma* 1-29 – OR=2.63 (1.8-4.0) 30-39 – OR=2.69 (1.6-4.6) 40-49 – OR=3.93 (2.2-7.1) 50-59 – OR=4.62 (2.5-8.5) ≥60 – OR=5.63 (2.7-11.7) <u>Cigarettes/day (reference category: 1-9)</u> *Esophageal adenocarcinoma* 10-19 – OR=1.30 (0.8-2.2) 20-29 – OR=1.33 (0.7-2.4) 30-39 – OR=1.65 (0.8-3.4) ≥40 – OR=1.34 (0.6-2.9) *Esophageal squamous cell carcinoma* 10-19 – OR=1.42 (0.9-2.3) 20-29 – OR=0.89 (0.5-1.6) 30-39 – OR=1.03 (0.5-2.1) ≥40 – OR=0.71 (0.3-1.5)
Oze, 2012[40]	EC (risk)	MEDLINE (1950-2011), Ichushi (1983-2011) Citation tracking	*Using the following as keywords: cigarette, smoking, esophagus, esophageal cancer, cohort, follow-up, case-control, Japan and Japanese* Restricted to studies conducted on Japanese populations and published in English or Japanese.	15 4 cohort 11 case-control	No	<u>Ever *vs.* never smokers</u> All studies – RR=3.01 (2.30-3.94), n=13, I^2=72%, Egger test: p=0.148 Only cohort studies – RR=2.97 (2.12-4.16), n=4 Only adjusted estimates for alcohol drinking – RR=2.70 (1.64-4.45), n=6, I^2=82% <u>Current *vs.* never smokers</u> All studies – RR=3.73 (2.16-6.43), n=7, I^2=78% Only cohort studies – RR=4.20 (2.83-6.23), n=3

						Former *vs.* never smokers All studies – RR=2.21 (1.60-3.06), n=7
Prabhu, 2013[32]	ESCC (risk)	MEDLINE (1948-2013), EBM reviews (inception-2013), EMBASE (1947-2011), ISI Web of Knowledge (inception-2013), BIOSIS preview (1926-2013)	*Key index terms for our literature review included {esophageal carcinoma, esophageal neoplasm or [esophagus and (squamous cell carcinoma, carcinoma, cancer, neoplasms, adenosquamous carcinoma or basosquamous carcinoma)]} and (risk factors, tobacco, tobacco smokeless, tobacco use disorder, tobacco smoke pollution, smoke, smoking, marijuana smoking, cigarette, cigar, alcohols, alcohol, alcohol drinking, alcoholism, alcohol abuse, ethanol, alcoholic beverages, liquor, beer, wine, spirits, or alcoholic intoxication), also using the alternative spelling 'oesophageal' or 'oesophagus'* No language restrictions	29 8 cohort 21 case-control	Newcastle-Ottawa Scale 13 highest quality studies	<u>Current *vs.* never smokers</u> All studies – OR=3.13 (2.53-3.86), n=29, I^2=87% Only highest quality studies – OR=2.95 (2.20-3.96), n=13, I^2=88% ACCORDING TO STUDY DESIGN Cohort – OR=2.74 (1.88-3.99), n=8, I^2=92% Case-control – OR=3.30 (2.62-4.16), n=21, I^2=76% ACCORDING TO RACE/CONTINENT Asia – OR=2.31 (1.78-2.99), n=12, I^2=86% (East Asia – OR=2.33 (1.73-3.15), n=10, I^2=87%) Europe – OR=4.21 (3.13-5.66), n=12, I^2=71% (Southern Europe – OR=3.69 (2.81-4.84), n=5, I^2=27%) (Northern Europe – OR=4.71 (2.37-9.37), n=5, I^2=86%) South America – OR=3.29 (1.75-6.18), n=3, I^2=56% <u>Ex- *vs.* never smokers</u> All studies – OR=1.68 (1.44-1.96), n=27, I^2=58% <u>≥20 cigarettes/day *vs.* never smokers</u> All studies – OR=3.66 (2.73-4.90), n=21, I^2=86% Only highest quality studies – OR=2.89 (1.78-4.71), n=8, I^2=89% ACCORDING TO STUDY DESIGN Cohort – OR=2.11 (1.33-3.33), n=6, I^2=86% Case-control – OR=4.62 (3.42-6.24), n=15, I^2=75% ACCORDING TO RACE/CONTINENT Asia – OR=2.52 (1.78-3.57), n=9, I^2=81% (East Asia – OR=2.63 (1.78-3.88), n=8, I^2=84%) Europe – OR=4.42 (3.23-6.06), n=9, I^2=61% (Southern Europe – OR=4.99 (3.42-7.28), n=5, I^2=52%)

							<u><20 cigarettes/day *vs.* never smokers</u> All studies – OR=1.84 (1.46-2.32), n=21, I^2=70% <u>≥20 years of smoking *vs.* never smokers</u> All studies – OR=2.81 (2.06-3.83), n=13, I^2=87% Only highest quality studies – OR=2.46 (1.35-4.48), n=3, I^2=96% Case-control studies – OR=2.92 (2.26-3.77), n=11, I^2=63% ACCORDING TO RACE/CONTINENT Asia – OR=2.34 (1.57-3.50), n=6, I^2=90% (East Asia – OR=2.92 (1.14-7.46), n=3, I^2=92%) Europe – OR=3.31 (2.15-5.10), n=6, I^2=56% (Southern Europe – OR=3.57 (1.76-7.25), n=3, I^2=72%) <u><20 years of smoking *vs.* never smokers</u> All studies – OR=1.67 (1.29-2.17), n=14, I^2=63%
Drahos, 2015[34]	EAC (risk)	International BEACON Consortium	NA		8 case-control	NA	<u>Current *vs.* never smokers</u> All age groups – OR=2.65 (2.17-3.24) ACCORDING TO AGE GROUP < 50 years – OR=2.72 (1.11-6.65) 50-59 years – OR=3.75 (2.46-5.69) 60-69 years – OR=1.81 (1.30-2.54) ≥ 70 years – OR=2.80 (1.93-4.07) <u>Former *vs.* never smokers</u> All age groups – OR=2.36 (1.94-2.88) ACCORDING TO AGE GROUP < 50 years – OR=2.44 (0.88-6.74) 50-59 years – OR=2.95 (1.89-4.62) 60-69 years – OR=1.86 (1.33-2.60) ≥ 70 years – OR=2.51 (1.80-3.49) <u>< 14 pack-years *vs.* never smokers</u> All age groups – OR=1.27 (1.05-1.55) ACCORDING TO AGE GROUP

						< 50 years – OR=2.02 (1.10-3.68) 50-59 years – OR=1.47 (0.96-2.25) 60-69 years – OR=0.98 (0.69-1.38) ≥ 70 years – OR=1.39 (0.99-1.96) <u>14 - > 30 pack-years *vs.* never smokers</u> All age groups – OR=2.01 (1.66-2.45) ACCORDING TO AGE GROUP < 50 years – OR=3.62 (2.04-6.42) 50-59 years – OR=2.13 (1.41-3.23) 60-69 years – OR=1.79 (1.28-2.50) ≥ 70 years – OR=1.66 (1.14-2.42) <u>30 - >45 pack-years *vs.* never smokers</u> All age groups – OR=2.00 (1.63-2.45) ACCORDING TO AGE GROUP < 50 years – OR=2.88 (1.35-6.14) 50-59 years – OR=2.35 (1.54-3.59) 60-69 years – OR=1.42 (1.00-2.01) ≥ 70 years – OR=2.11 (1.45-3.07) <u>≥ 45 pack-years *vs.* never smokers</u> All age groups – OR=2.50 (2.09-3.00) ACCORDING TO AGE GROUP < 50 years – OR=2.68 (1.10-6.53) 50-59 years – OR=3.41 (2.29-5.07) 60-69 years – OR=1.84 (1.36-2.48) ≥ 70 years – OR=2.61 (1.92-3.54)
Fahey, 2015[28]	ESCC, EAC (mortality)	MEDLINE (inception-2014), EMBASE (inception-2014) Citation tracking	("Esophagus"[Mesh] OR "Esophagus"[Title/Abstract] OR "Oesophagus"[Title/Abstract] OR "Esophageal"[Title/Abstract] OR "Oesophageal"[Title/Abstract]) AND ("Neoplasms"[Mesh] OR "Neoplasm"[Title/Abstract] OR "Cancer*"[Title/Abstract] OR "Carcinoma"[Title/Abstract] OR "Adenocarcinoma"[Title/Abstract]) AND (("Survival" [Mesh]) OR ("Prognosis" [Mesh]) OR ("survival" [Title/Abstract]) OR ("prognosis" [Title/Abstract]) OR ("prognostic" [Title/Abstract])) AND (("smoking" [Title/Abstract]) OR ("tobacco" [Title/Abstract]) OR ("alcohol" [Title/Abstract]) OR ("physical activity"	12	JAMA	<u>Ever *vs.* never smokers</u> *ESCC* HR=1.19 (1.04-1.36), n=6, I^2=47.0% *EAC* HR=0.96 (0.82-1.12), n=4, I^2=0.0% <u>Highest *vs.* lowest pack-years</u> *ESCC*

			[Title/Abstract]) OR ("exercise" [Title/Abstract]) OR ("sedentary lifestyle"[Title/Abstract]) OR ("body mass index"[Title/Abstract]) OR ("BMI" [Title/Abstract]) OR ("obesity" [Title/Abstract]) OR ("Aspirin"[Title/Abstract]) OR ("Non-Steroidal Anti-Inflammatory"[Title/Abstract]) OR ("NSAID"[Title/Abstract]) OR ("health behavior"[Title/Abstract]) OR ("health behaviour"[Title/Abstract]) OR ("life style"[Title/Abstract]) OR ("lifestyle"[Title/Abstract]) OR ("life-style"[Title/Abstract]) OR ("Smoking"[Mesh]) OR ("Alcohol Drinking"[Mesh]) OR ("Motor Activity"[Mesh]) OR ("Exercise"[Mesh]) OR ("Sedentary Lifestyle"[Mesh]) OR ("Body Mass Index"[Mesh]) OR ("Obesity"[Mesh]) OR ("Health Behavior"[Mesh]) OR ("Life Style"[Mesh]) OR ("Aspirin"[Mesh]) OR ("Anti-Inflammatory Agents, Non-Steroidal"[Mesh])) Restricted to studies published in English			HR=1.55 (1.24-1.94), n=4, I^2=0.0% No evidence of publication bias
SMOKELESS TOBACCO						
Boffetta, 2008[47]	EC (risk)	Studies included in IARC Monograph, plus MEDLINE and PubMed (2004-2007) Citation tracking	("snus", "snuff" OR "smokeless tobacco") AND ("cancer" OR "neoplasm")	5 2 cohort 3 case-control	Not stated	<u>Ever *vs.* never smokeless tobacco users</u> All studies – RR=1.6 (1.1-2.3), n=5 ACCORDING TO GEOGRAPHIC AREA USA – RR=1.2 (0.1-13.0), n=1 Nordic countries – RR=1.6 (1.1-2.4), n=4
Lee, 2009[48]	EC (risk)	MEDLINE (inception-2008) Citation tracking	*"cancer" AND ("smokeless tobacco" OR "chewing tobacco" OR "snuff" OR "alcohol")* Restricted to studies conducted in Europe and North America	14 4 cohort 10 case-control	No	<u>Smokeless tobacco (any type)</u> Overall data – RR=1.25 (1.03-1.51), n=10, I^2=13.0% Smoking adjusted – RR=1.13 (0.95-1.36), n=7, I^2=0.0% Never smokers – RR=1.91 (1.15-3.17), n=4, I^2=0.0% <u>Smokeless tobacco (any type in USA)</u> Overall data – RR=1.56 (1.11-2.19), n=6, I^2=4.6% Smoking adjusted – RR=1.89 (0.84-4.25), n=3, I^2=0.0% Never smokers – RR=1.89 (0.84-4.25), n=3, I^2=0.0% <u>Smokeless tobacco (snuff in Scandinavia)</u> Overall data – RR=1.10 (0.92-1.33), n=4, I^2=0.0%

						Smoking adjusted – RR=1.10 (0.92-1.33), n=4, I^2=0.0% Never smokers – RR=1.92 (1.00-3.68), n=1
Lee, 2011[46]	EC, ESCC, EAC (risk)	MEDLINE (inception-2010) Citation tracking	*"cancer" AND ("smokeless tobacco" OR "chewing tobacco" OR "snuff" OR "snus")* All studies conducted in Sweden and one in Norway	4 2 cohort 2 case-control	No	<u>Ever vs. never snus users</u> Whole population – RR=1.10 (0.92-1.33), n=4 ACCORDING TO HISTOLOGICAL TYPE EAC – RR=1.0 (0.6-1.5) ESCC – RR=1.0 (0.8-1.4) Never smokers – RR=1.92 (1.00-3.68), n=1 ACCORDING TO HISTOLOGICAL TYPE EAC – RR=0.2 (0.0-1.9) ESCC – RR=3.5 (1.6-7.6)
Akhtar, 2013[45]	ESCC (risk)	MEDLINE, EMBASE (inception-2012) Citation tracking	*using the search terms case–control and/or cohort study, areca nut, betel nut, betel quid without tobacco, combined with oesophageal squamous-cell carcinoma, oesophageal cancer, chewing, and Asia* No language restrictions	12 case-control	No	<u>Areca nut chewing in Asians</u> OR=3.05 (2.41-3.87), n=12, I^2=55%, Egger test: p=0.289 ACCORDING TO SEX Only men – OR=2.99 (1.83-4.88), n=4, I^2=61% Men and women – OR=3.09 (2.32-4.11), n=8, I^2=62% <u>Additive interaction between areca nut chewing and tobacco smoking</u> OR=6.79 (4.71-9.79), n=6
Siddiqi, 2015[49]	EC (risk)	MEDLINE, EMBASE, PsycINFO, CINAHL Plus, ISI Web of Knowledge, SCOPUS, COCHRANE, AJOL, LILACS, WHO, PakMediNet, IndMED, ProQuest, EThOS, Open Grey	*by combining an exhaustive list of terms for smokeless tobacco with terms for specific cancers and cardiovascular disease outcomes* No language restrictions	12 2 cohort 10 case-control	Newcastle-Ottawa Scale	<u>Ever *vs.* never smokeless tobacco use</u> All studies – OR=2.17 (1.70-2.78), n=12, I^2=76% ACCORDING TO GEOGRAPHIC AREA India – OR=2.57 (2.20-3.00), n=7, I^2=22% Pakistan – OR=8.20 (2.45-27.47), n=2, I^2=67% Norway – OR=1.40 (0.61-3.21), n=1 Sweden – OR=1.26 (1.02-1.56), n=5, I^2=0% North America – OR=1.20 (0.10-14.40), n=1

		(inception-2015) Citation tracking				
SMOKING AND ALCOHOL						
Castellsagué, 1999[26]	ESCC (risk)	Pooled analysis of hospital-based case-control studies conducted in high-risk areas in South America	NA	5 case-control	NA	<u>Joint effects</u> *Never drinkers/Ever smokers* All – OR=1.95 (1.35-2.82) Men – OR=4.45 (2.09-9.47) Women – OR=1.57 (0.89-2.75) *Ever drinkers/Never smokers* All – OR=1.75 (1.17-2.63) Men – OR=4.03 (1.76-9.21) Women – OR=1.42 (0.82-2.48) *Ever drinkers/Ever smokers* All – OR=8.00 (5.67-11.27) Men – OR=17.0 (8.36-34.78) Women – OR=7.26 (3.68-14.33)
Ansary-Moghaddam, 2009a[36]	EC (risk)	MEDLINE, EMBASE Citation tracking	*MeSH terms (all exploded): "esophageal", "laryngeal", "pharyngeal", or "oral cavity" together with "neoplasm", "squamous cell", "adenocarcinoma", or "cancer" together with "cohort study" or "case-control study"*	Not specified for EC	No	<u>Current *vs.* never smokers</u> *Non-drinkers* RR=2.45 (2.06-2.91) *Drinkers* RR=6.01 (3.82-9.44) <u>Joint effects</u> RR=10.0 (4.08-24.5)
Prabhu, 2014[4]	ESCC (risk)	MEDLINE (1948-2013), EBM reviews (inception-2013), EMBASE (1947-2013), ISI Web of Knowledge (inception-2013), BIOSIS (1926-2013)	*((esophageal or esophagus or esophageal neoplasm) and (squamous cell carcinoma, carcinoma, cancer, neoplasm, adenosquamous carcinoma, or basosquamous carcinoma)) and (risk factors, tobacco, tobacco smokeless, tobacco use disorder, tobacco smoke pollution, smoke, smoking, marijuana smoking, cigarette, cigar, alcohols, alcohol, alcohol drinking, alcoholism, alcohol abuse, ethanol, alcoholic beverages, liquor, beer, wine, spirits, alcoholic intoxication)* No language restrictions	5 2 cohort 3 case-control	Newcastle-Ottawa Scale	<u>Synergy factors</u> *Alcohol non-use/Tobacco use* OR=1.36 (1.14-1.61), n=5, I^2=0.00% *Alcohol use/Tobacco non-use* OR=1.21 (0.81-1.81), n=5, I^2=34.41% *Alcohol use/Tobacco use* OR=3.28 (2.11-5.08), n=5, I^2=55.30% Cohort – OR=4.47 (2.62-7.63), n=3, I^2=0.00% Case-control – OR=3.53 (1.71-7.27), n=2, I^2=39.21% SF=1.85 (1.45-2.38), n=5, I^2=11.15%

		Citation tracking				
SMOKING, ALCOHOL AND GREEN TEA						
Ishikawa, 2006[17]	EC (incidence)	Pooled analysis of prospective cohort studies conducted in Miyagi Prefecture, Japan	NA	2 cohort	NA	Currently smoking, Daily alcohol drinking, Daily consumption of ≥ 3 cups/day of green tea -/+/- : HR=2.61 (0.42-16.07) -/-/+: HR=1.65 (0.29-9.19) +/+/-: HR=9.23 (2.10-40.60) +/-/+: HR=4.99 (1.11-22.43) -/+/+: HR=2.97 (0.53-16.58) +/+/+: HR=11.1 (2.63-46.51)
HELICOBACTER PYLORI INFECTION						
Rokkas, 2007[51]	ESCC, EAC (risk)	MEDLINE, EMBASE (inception-2007) Citation tracking	*helicobacter pylori AND (esophageal cancer OR esophageal neoplasms OR Barrett's esophagus OR adenocarcinoma OR squamous cell carcinoma)* Restricted to studies published in English	18 9 cohort 9 case-control	No	*EAC* *H. pylori* infected *vs.* uninfected OR=0.52 (0.37-0.73), n=10, I^2=34.6%, Begg test: p=0.37 *CagA* infected *vs.* uninfected OR=0.51 (0.31-0.82), n=6, I^2=0.0%, Begg test: p=0.26 *ESCC* *H. pylori* infected *vs.* uninfected OR=0.86 (0.56-1.33), n=5, I^2=84.7%, Begg test: p=0.80 *CagA* infected *vs.* uninfected OR=1.22 (0.70-2.13), n=3, I^2=73.4%, Begg test: p=0.30
Islami, 2008[50]	ESCC, EAC (risk)	MEDLINE, WEB OF SCIENCE (inception-2008) Citation tracking	*("Helicobacter pylori" [MeSH] OR (Campylobacter pylori) OR (H Pylori) OR (H. Pylori)) AND ("Esophageal Neoplasms"[MeSH] OR (Cancer of Esophagus) OR (Cancer of the Esophagus) OR (Esophageal Cancer) OR (Esophagus Cancer) OR (Esophagus Neoplasm) OR (Neoplasms, Esophageal)); the search was repeated by replacing Esophagus with Oesophagus, and Esophageal with Oesophageal*	19 case-control	No	*EAC* *H. pylori* infected *vs.* uninfected All studies – OR=0.56 (0.46-0.68), n=13, I^2=15%, Egger test: p=0.71, Begg test: p=0.76 Large studies – OR=0.58 (0.47-0.73), n=8, I^2=27% Population-based studies – OR=0.58 (0.43-0.76), n=6, I^2=32% Western studies – OR=0.57 (0.47-0.70), n=12, I^2=17%

						Eastern studies – OR=0.32 (0.10-1.02), n=1 Serologic studies – OR=0.59 (0.48-0.73), n=10, I^2=10% Adjusted results – OR=0.50 (0.34-0.74), n=7, I^2=28% <u>*CagA* infected *vs.* uninfected</u> OR=0.41 (0.28-0.62), n=5, I^2=16% *ESCC* <u>*H. pylori* infected *vs.* uninfected</u> All studies – OR=1.10 (0.78-1.55), n=9, I^2=73%, Egger test: p=0.84, Begg test: p=0.47 Large studies – OR=1.10 (0.78-1.55), n=9, I^2=73% Population-based studies – OR=1.00 (0.62-1.60), n=6, I^2=82% Western studies – OR=1.17 (0.71-1.95), n=4, I^2=63% Eastern studies – OR=1.05 (0.63-1.77), n=5, I^2=81% Serologic studies – OR=1.10 (0.78-1.55), n=9, I^2=73% Adjusted results – OR=0.99 (0.67-1.45), n=7, I^2=56% <u>*CagA* infected *vs.* uninfected</u> OR=1.01 (0.80-1.27), n=4, I^2=0%
Zhuo, 2008[53]	EC, ESCC, EAC (risk)	MEDLINE, EMBASE, CNKI (1989-2007) Citation tracking	*Helicobacter pylori and oesophageal cancer* No language restrictions	12 case-control	No	*EAC* <u>*H. pylori* infected *vs.* uninfected</u> OR=0.58 (0.48-0.70), n=9, I^2=40.6%, Egger test: p=0.69 <u>*CagA* infected *vs.* uninfected</u> OR=0.54 (0.40-0.73), n=6, I^2=0.0% *ESCC* <u>*H. pylori* infected *vs.* uninfected</u> OR=0.80 (0.45-1.43), n=5, I^2=85.1% <u>*CagA* infected *vs.* uninfected</u> OR=1.20 (0.45-3.18), n=2, I^2=90.4%

						EC <u>*CagA* infected *vs.* uninfected</u> OR=0.69 (0.45-1.05), n=7, I^2=67.9%
Xie, 2013[52]	ESCC, EAC (risk)	MEDLINE (inception-2013) Citation tracking	*"Helicobacter pylori" [MeSH] OR (Campylobacter pylori) OR (H. pylori) OR (H. pylori) AND ("Esophageal Neoplasms" [MeSH] OR (Cancer of Esophagus) OR (Cancer of the Esophagus) OR (Esophageal Cancer) OR (Esophagus Cancer) OR (Esophagus Neoplasm) OR (Neoplasms, Esophageal)*	27 case-control	No	*EAC* <u>*H. pylori* infected *vs.* uninfected</u> All studies – OR=0.59 (0.51-0.68), n=15, I^2=29.9%, Egger test: p=0.371, Begg test: p=0.621 Population-based studies – OR=0.62 (0.52-0.73), n=8, I^2=40.9% Clinical-based studies – OR=0.53 (0.40-0.68), n=7, I^2=14.5% Eastern studies – OR=0.32 (0.10-1.02), n=1 Western studies – OR=0.60 (0.52-0.68), n=14, I^2=31.0% Adjusted results – OR=0.51 (0.40-0.61), n=8, I^2=28.6% <u>*CagA* infected *vs.* uninfected</u> All/Western studies – OR=0.56 (0.45-0.70), n=8, I^2=39.9% *ESCC* <u>*H. pylori* infected *vs.* uninfected</u> All studies – OR=0.83 (0.63-1.03), n=16, I^2=74.5%, Egger test: p=0.424, Begg test: p=0.753 Population-based studies – OR=0.79 (0.59-1.00), n=14, I^2=76.0% Clinical-based studies – OR=1.49 (0.66-2.31), n=2, I^2=0.0% Eastern studies – OR=0.66 (0.43-0.89), n=8, I^2=79.5% Western studies – OR=1.02 (0.80-1.25), n=8, I^2=1.2% Adjusted results – OR=0.84 (0.56-1.12), n=11, I^2=80.5% <u>*CagA* infected *vs.* uninfected</u> All studies – OR=0.97 (0.76-1.24), n=9, I^2=52.0% Eastern studies – OR=0.77 (0.65-0.92), n=3, I^2=35.0% Western studies – OR=1.26 (0.97-1.63), n=6, I^2=3.6%

Nie, 2014[54]	ESCC, EAC (risk)	MEDLINE, ISI WEB OF KNOWLEDGE, CBD, WANFANG, CNKI (inception-2013) Citation tracking	*Using the key words 'Helicobacter pylori', 'H. pylori', or 'HP', and 'esophageal neoplasm', 'esophageal carcinoma', 'esophageal tumor', 'esophageal cancer', 'esophageal squamous cell carcinoma', 'esophageal squamous carcinoma', 'ESCC', 'esophageal adenocarcinoma', 'adenocarcinoma of the esophagus', or 'EAC'* Restricted to studies published in English or Chinese	28 case-control	Newcastle-Ottawa scale	*ESCC* <u>*H. pylori* infected *vs.* uninfected</u> OR=1.16 (0.83-1.60), n=19, I^2=85.7%, Egger test: p=0.280 <u>*CagA* infected *vs.* uninfected</u> OR=1.01 (0.73-1.40), n=7, I^2=49.7% Egger test: p=0.496 *EAC* <u>*H. pylori* infected *vs.* uninfected</u> OR=0.57 (0.44-0.73), n=13, I^2=53.3% Egger test: p=0.216 <u>*CagA* infected *vs.* uninfected</u> OR=0.64 (0.52-0.79), n=7, I^2=0.0% Egger test: p=0.170
GERD						
Rubenstein, 2010[55]	EAC (risk)	MEDLINE (1950-2008), EMBASE (1947-2008), WEB OF SCIENCE (1900-2008), COCHRANE (2008), BIOSIS (1926-2008), DARE (2008), ACP (1991-2008) Citation tracking	*['gastroesophageal reflux', or 'GERD', or 'oesophageal reflux', or 'oesophagitis', or 'heartburn', or 'pyrosis', or 'regurgitation'] and ['oesophageal neoplasm', or 'adenocarcinoma', or 'carcinoma', or 'Barrett*', or 'metaplasia', or 'metaplastic']*	5 case-control	No	<u>Weekly gastro-oesophageal reflux symptoms *vs.* less frequent or no symptoms</u> OR=4.92 (3.90-6.22), n=5, I^2=60% Men – OR=4.3 (3.3-5.7), n=1 Women – OR=3.5 (1.9-6.6), n=1 <u>Daily gastro-oesophageal reflux symptoms *vs.* symptoms less than weekly or no symptoms</u> OR=7.40 (4.94-11.1), n=5, I^2=71% <u>Symptoms of at least 20 years of duration</u> OR=5.41 (2.45-11.9), n=4, I^2=89% <u>Symptoms of less than 10-15 years of duration</u> OR=3.05 (1.53-6.08), n=4, I^2=84%
Cook, 2014[56]	EAC (risk)	International BEACON Consortium	NA	5 case-control	NA	<u>Recurrent *vs.* not-recurrent heartburn</u> OR=4.64 (3.28-6.57), I^2=74% <u>Recurrent *vs.* not-recurrent regurgitation</u> OR=4.57 (3.43-6.08), I^2=55%

							Recurrent *vs.* not-recurrent heartburn or regurgitation OR=4.81 (3.39-6.82), I^2=76% Heartburn duration (years) *vs.* never 0.1-<10 – OR=2.80 (1.60-4.91), I^2=68% 10-<20 – OR=3.85 (2.93-5.07), I^2=0% ≥20 – OR=6.24 (3.37-11.55), I^2=85% Regurgitation duration (years) *vs.* never 0.1-<10 – OR=2.69 (1.49-4.83), I^2=75% 10-<20 – OR=4.18 (2.37-7.37), I^2=71% ≥20 – OR=4.39 (2.34-8.25), I^2=84% Heartburn and regurgitation duration (years) *vs.* never 0.1-<10 – OR=3.48 (1.56-7.73), I^2=82% 10-<30 – OR=3.97 (2.41-6.54), I^2=72% ≥30 – OR=6.08 (3.26-11.34), I^2=83% Heartburn frequency *vs.* never <Monthly – OR=0.91 (0.68-1.21), I^2=0% Monthly-<Weekly – OR=2.90 (1.78-4.72), I^2=56% Weekly-<Daily – OR=4.20 (2.76-6.40), I^2=68% ≥Daily – OR=7.42 (4.23-13.02), I^2=76% Regurgitation frequency *vs.* never <Monthly – OR=0.71 (0.48-1.04), I^2=37% Monthly-<Weekly – OR=3.13 (2.14-4.58), I^2=40% Weekly-<Daily – OR=5.07 (3.51-7.32), I^2=55% ≥Daily – OR=4.94 (3.37-7.24), I^2=35% Heartburn and regurgitation frequency *vs.* never ≤Weekly – OR=2.08 (1.14-3.79), I^2=86% >Weekly-Daily – OR=5.07 (3.07-8.38), I^2=75% >Daily – OR=7.96 (4.51-14.04), I^2=73%
Drahos, 2015[34]	EAC (risk)	International BEACON Consortium	NA		8 case-control	NA	Recurrent *vs.* not-recurrent heartburn All age groups – OR=4.52 (3.84-5.33) ACCORDING TO AGE GROUP < 50 years – OR=6.62 (3.66-11.97) 50-59 years – OR=3.17 (2.19-4.60) 60-69 years – OR=5.03 (3.82-6.64)

≥ 70 years – OR=5.21 (3.88-6.99)

Recurrent *vs.* not-recurrent regurgitation
All age groups – OR=4.45 (3.74-5.31)

ACCORDING TO AGE GROUP
< 50 years – OR=7.98 (4.26-14.96)
50-59 years – OR=3.31 (2.20-4.98)
60-69 years – OR=4.38 (3.27-5.85)
≥ 70 years – OR=5.24 (3.81-7.19)

Recurrent *vs.* not-recurrent heartburn or regurgitation
All age groups – OR=4.70 (4.03-5.49)

ACCORDING TO AGE GROUP
< 50 years – OR=8.06 (4.52-14.37)
50-59 years – OR=3.15 (2.22-4.45)
60-69 years – OR=5.33 (4.08-6.95)
≥ 70 years – OR=5.20 (3.95-6.85)

Heartburn frequency – < monthly *vs.* never:
All age groups – OR=0.88 (0.67-1.16)

ACCORDING TO AGE GROUP
< 50 years – OR=0.55 (0.21-1.49)
50-59 years – OR=0.65 (0.39-1.11)
60-69 years – OR=1.08 (0.68-1.71)
≥ 70 years – OR=0.86 (0.51-1.44)

Heartburn frequency – monthly to < weekly *vs.* never:
All age groups – OR=2.74 (2.10-3.57)

ACCORDING TO AGE GROUP
< 50 years – OR=1.87 (0.61-5.75)
50-59 years – OR=1.93 (1.14-3.27)
60-69 years – OR=3.69 (2.35-5.80)
≥ 70 years – OR=2.63 (1.63-4.26)

Heartburn frequency – weekly to < daily *vs.* never:
All age groups – OR=4.15 (3.35-5.15)

	ACCORDING TO AGE GROUP < 50 years – OR=5.21 (2.45-11.06) 50-59 years – OR=2.52 (1.51-4.18) 60-69 years – OR=5.27 (3.64-7.61) ≥ 70 years – OR=4.25 (2.93-6.15) <u>Heartburn frequency – ≥ daily *vs.* never</u>: All age groups – OR=7.04 (5.47-9.08) ACCORDING TO AGE GROUP < 50 years – OR=6.84 (2.92-16.02) 50-59 years – OR=4.65 (2.72-7.94) 60-69 years – OR=7.75 (5.02-11.97) ≥ 70 years – OR=11.41 (7.04-18.48) <u>Regurgitation frequency – < monthly *vs.* never</u>: All age groups – OR=0.70 (0.55-0.91) ACCORDING TO AGE GROUP < 50 years – OR=0.52 (0.21-1.26) 50-59 years – OR=0.56 (0.34-0.91) 60-69 years – OR=0.73 (0.47-1.14) ≥ 70 years – OR=0.75 (0.46-1.22) <u>Regurgitation frequency – monthly to < weekly *vs.* never</u>: All age groups – OR=2.82 (2.21-3.59) ACCORDING TO AGE GROUP < 50 years – OR=2.36 (0.88-6.32) 50-59 years – OR=2.21 (1.31-3.74) 60-69 years – OR=2.59 (1.70-3.92) ≥ 70 years – OR=3.69 (2.43-5.62) <u>Regurgitation frequency – weekly to < daily *vs.* never</u>: All age groups – OR=5.03 (4.02-6.31) ACCORDING TO AGE GROUP < 50 years – OR=7.03 (3.22-15.33) 50-59 years – OR=3.27 (1.95-5.49) 60-69 years – OR=5.65 (3.87-8.23) ≥ 70 years – OR=5.65 (3.77-8.46)

						Regurgitation frequency – ≥ daily *vs.* never: All age groups – OR=4.83 (3.64-6.42) ACCORDING TO AGE GROUP < 50 years – OR=7.00 (2.53-19.40) 50-59 years – OR=3.25 (1.65-6.40) 60-69 years – OR=4.33 (2.70-6.94) ≥ 70 years – OR=6.58 (3.99-10.86) Heartburn or regurgitation frequency – monthly to < weekly *vs.* never: All age groups – OR=1.28 (1.04-1.59) ACCORDING TO AGE GROUP < 50 years – OR=1.23 (0.57-2.65) 50-59 years – OR=0.79 (0.51-1.21) 60-69 years – OR=1.63 (1.11-2.39) ≥ 70 years – OR=1.42 (0.97-2.07) Heartburn or regurgitation frequency – weekly to < daily *vs.* never: All age groups – OR=4.40 (3.57-5.44) ACCORDING TO AGE GROUP < 50 years – OR=7.05 (3.23-15.41) 50-59 years – OR=2.25 (1.39-3.64) 60-69 years – OR=5.95 (4.09-8.67) ≥ 70 years – OR=4.56 (3.20-6.51) Heartburn or regurgitation frequency – ≥ daily *vs.* never: All age groups – OR=6.86 (5.41-8.70) ACCORDING TO AGE GROUP < 50 years – OR=9.59 (3.97-23.18) 50-59 years – OR=4.01 (2.40-6.73) 60-69 years – OR=8.16 (5.39-12.34) ≥ 70 years – OR=9.55 (6.24-14.62)
BARRETT'S ESOPHAGUS (BE)						
Thomas, 2007[57]	EC, EAC (incidence)	MEDLINE, EMBASE	*Using key words ' BO', 'short segment Barrett's oesophagus' (SSBO), 'oesophageal (oesophageal) cancer'*	41 cohort	No	*EC* Prev=4% (2.6-5.4), n=39

		(1966-2004) Citation tracking	*(both American and British spellings used), 'oesophageal ⁄ oesophageal neoplasm' and 'surveillance'* Restricted to studies published in English			IR=7/1000 pyd (6-9), n=41 Egger test: p=0.18; Begg test: p=0.17 ACCORDING TO GEOGRAPHIC AREA USA – IR=7/1000 pyd (4-9), n=16 UK – IR=7/1000 pyd (4-12), n=13 Europe – IR=8/1000 pyd (5-12), n=10 Australia/New Zealand – IR=5/1000 pyd (1-25), n=2 *EAC* Short segment BE *vs.* conventional BE RR=0.55 (0.19-1.60), n=6
BODY MASS INDEX (BMI)						
Hampel, 2005[61]	EAC (risk)	MEDLINE (inception-2004) Citation tracking	*Search terms included obesity or body mass or anthroprometry searched with reflux or heartburn, (o)esophagitis, Barrett's or Barretts, and (o)esophageal cancer or (o)esophageal adenocarcinoma* Restricted to studies published in English	7 case-control	No	Overweight/Obese *vs.* Normal weight OR=2.02 (1.53-2.67), n=6, no evidence of publication bias Overweight *vs.* Normal weight OR=1.52 (1.15-2.01), n=6, no evidence of publication bias Obese *vs.* Normal weight OR=2.78 (1.85-4.16), n=6, no evidence of publication bias
Kubo, 2006[63]	EAC (risk)	MEDLINE (1966-2005), WEB OF SCIENCE (not stated) Citation tracking	*[esophag* AND (adenocarcinoma OR carcinoma OR cancer)] combined with ''body mass index OR BMI OR obesit.'; similar search was done using the word ''oesophagus,'' a common British spelling for esophagus; identical searches were done using ''cardia'' AND (adenocarcinoma OR carcinoma OR cancer)* No language restrictions	7 1 cohort 6 case-control	No	Overweight/Obese *vs.* Normal weight All studies – OR=2.1 (1.7-2.4), n=7, Begg test: p=0.52 ACCORDING TO SEX Men – OR=2.2 (1.8-2.7), n=4 Women – OR=1.9 (1.5-2.5), n=5 Overweight *vs.* Normal weight All studies – OR=1.9 (1.5-2.4), n=6 ACCORDING TO SEX Men – OR=1.8 (1.5-2.2), n=3 Women – OR=1.5 (1.1-2.2), n=3 Obese *vs.* Normal weight All studies – OR=2.4 (2.0-2.8), n=6

						ACCORDING TO SEX Men – OR=2.4 (1.9-3.2), n=3 Women – OR=2.1 (1.4-3.2), n=3
WCRF, 2007[22]	ESCC, EAC (risk, incidence, mortality)	MEDLINE, WEB OF SCIENCE, CINAHL, BIOSIS, CAB Abstracts, LILACS, EMBASE COCHRANE (inception-2006) Citation tracking	*Not specifically stated* No language restrictions	7 1 cohort 6 case-control	No	<u>Per 1 Kg/m^2 increment in BMI</u> *ESCC/Mixed/Unspecified* Cohort – RR=1.07 (1.00-1.14), n=1 Case-control – RR=0.98 (0.90-1.08), n=3, I^2=90.4% *EAC* Case-control – RR=1.11 (1.07-1.15), n=5, I^2=40.1%
Renehan, 2008[59]	ESCC, EAC (incidence)	MEDLINE (inception-2007), EMBASE (inception-2007) Citation tracking	*Our core search consisted of terms related to bodyweight ("obesity", "adiposity", "body mass index", and "body size"), combined with specific terms for each cancer site* No language restrictions	6 5 cohort 1 nested case-control	Methodological quality was assessed according to three study components which might affect the strength of the association between BMI and cancer risk: length of follow-up; whether BMI was self-reported or measured; and the extent of adjustments for potential confounding factors	<u>Increase of 5 Kg/m^2 in BMI</u> *EAC* ACCORDING TO SEX Men – RR=1.52 (1.33-1.74), n=5, I^2=24% Women – RR=1.51 (1.31-1.74), n=3, I^2=0% *ESCC* ACCORDING TO SEX Men – RR=0.71 (0.60-0.85), n=3, I^2=49% Women – RR=0.57 (0.47-0.69), n=2, I^2=60%
Smith, 2008[60]	ESCC, EAC (risk)	MEDLINE (1980-2006), EMBASE (1980-2006)	Not stated Restricted to studies published in English	14 5 cohort 9 case-control	No	<u>Increase of 5 Kg/m^2 in BMI</u> *EAC* ACCORDING TO STUDY DESIGN Cohort – RR=1.53 (1.30-1.79), n=1

		Citation tracking				Case-control – RR=1.54 (1.39-1.71), n=6 *ESCC* ACCORDING TO STUDY DESIGN Cohort – RR=0.69 (0.63-0.75), n=3 Case-control – RR=0.49 (0.44-0.55), n=7
Guh, 2009[58]	EC (incidence)	MEDLINE, EMBASE (inception-2007) Citation tracking	*'Incidence, Prevalence, Risk, Risk Factors, Cohort Studies, Longitudinal Studies, Follow-up Studies, or Prospective Studies' in combination with 'Adipose Tissue, Obesity, Body Mass Index, or Body Composition' (all "exploded"); these same search terms were applied to each co-morbidity (also "exploded")* Restricted to studies published in English	1 cohort	No	<u>Overweight *vs.* Normal weight</u> Men – RR=1.13 (1.02-1.26), n=1 Women – RR=1.15 (0.97-1.36), n=1 <u>Obese *vs.* Normal weight</u> Men – RR=1.21 (0.97-1.52), n=1 Women – RR=1.20 (0.95-1.53), n=1
Hoyo, 2012[62]	EAC (risk)	International BEACON Consortium	NA	12 2 cohort 10 case-control	NA	<u>Overweight *vs.* Normal weight</u> All studies – OR=1.54 (1.26-1.88), n=12, I^2=55% ACCORDING TO SEX Men – OR=1.63 (1.32-2.00), I^2=51% Women – OR=1.24 (0.67-2.29), I^2=56% ACCORDING TO GERD No – OR=1.12 (0.80-1.58), I^2=0% Yes – OR=1.48 (1.07-2.05), I^2=40% <u>Obese Class I (30 ≤ BMI < 35) *vs.* Normal weight</u> All studies – OR=2.39 (1.86-3.06), n=12, I^2=42% ACCORDING TO SEX Men – OR=2.47 (1.94-3.13), I^2=26% Women – OR=2.66 (1.59-4.46), I^2=17% ACCORDING TO GERD No – OR=1.85 (0.91-3.73), I^2=48% Yes – OR=2.21 (1.44-3.39), I^2=37% <u>Obese Class II (35 ≤ BMI < 40) *vs.* Normal weight</u> All studies – OR=2.79 (1.89-4.12), n=11, I^2=23% ACCORDING TO SEX Men – OR=2.87 (1.89-4.36), I^2=17%

						Women – OR=1.38 (0.57-3.35), I^2=0% ACCORDING TO GERD No – OR=2.08 (1.00-4.30), I^2=0% Yes – OR=2.95 (1.15-7.59), I^2=49% <u>Obese Class III (BMI ≥ 40) *vs.* Normal weight</u> All studies – OR=4.76 (2.96-7.66), n=9, I^2=0% ACCORDING TO SEX Men – OR=4.47 (2.42-8.26), I^2=0% Women – OR=5.88 (2.28-15.10), I^2=0% ACCORDING TO GERD No – OR=6.45 (1.60-25.99), I^2=100% Yes – OR=5.84 (2.72-12.55), I^2=0% <u>Increment of 1 Kg/m^2 in BMI</u> All studies – OR=1.09 (1.06-1.12), n=12, I^2=76% ACCORDING TO SEX Men – OR=1.09 (1.06-1.13), I^2=76% Women – OR=1.07 (1.04-1.10), I^2=13% ACCORDING TO GERD No – OR=1.07 (1.03-1.11), I^2=0% Yes – OR=1.08 (1.03-1.14), I^2=71% <u>Interactions with body mass index</u> *EAC* Cigarette smoking – S=1.11 (0.87-1.40) Alcohol – S=1.31 (0.12-13.74) *H. pylori* (negative) – S=1.08 (0.37-3.20) Heartburn – S=1.42 (0.89-2.26) Reflux – S=1.20 (0.64-2.28) GERD – S=1.42 (1.04-1.94)
Dobbins, 2013[66]	EAC (risk)	Renehan, 2008 plus MEDLINE (2007-2011), EMBASE	*Our core search consisted of terms related to bodyweight ("obesity", "adiposity", "body mass index", and "body size"), combined with specific terms for each cancer site* No language restrictions	7	based on the work of the Evidence-based Medicine	<u>Obese *vs.* Normal weight</u> *EAC* ACCORDING TO SEX

		(2007-2011) Citation tracking	(replicated from Renehan, 2008)		group at McMaster University	Men – RR=1.23 (0.58-2.60), n=3, I^2=75% Women – RR=2.04 (1.18-3.55), n=4, I^2=78%
Singh, 2013[65]	EAC (risk)	MEDLINE (1966-2013), EMBASE (1988-2013), WEB OF SCIENCE (1993-2013) Citation tracking	*Medical subject heading (MeSH) terms used in the search included a combination of "Obesity", "Waist Circumference", "Waist-Hip Ratio", "Body Fat Distribution", "Adiposity", "Abdominal Fat", "Obesity, Abdominal" AND "Esophagitis", "Barrett esophagus" OR "esophageal neoplasm"* No language restrictions	6 3 cohort 3 case-control	Newcastle-Ottawa scale	<u>Central adiposity (highest *vs.* lowest category of exposure)</u> OR=2.51 (1.56-4.04), n=5, I^2=62%, Egger test: p=0.67 <u>BMI (highest *vs.* lowest category of exposure)</u> OR=2.45 (1.84-3.28), n=5
Turati, 2013[64]	EAC (risk)	MEDLINE (inception-2011) Citation tracking	*'body mass index' or 'BMI' or 'obesity' and combinations of 'esophageal neoplasms' or 'stomach neoplasms' and 'adenocarcinoma'* Restricted to studies published in English	18 8 cohort 10 case–control	No	<u>Overweight *vs.* Normal weight</u> RR=1.87 (1.61-2.17), n=17 <u>Obese *vs.* Normal weight</u> RR=2.73 (2.16-3.46), n=10 <u>Increment of 5 Kg/m^2 of BMI</u> RR=1.13 (1.11-1.16), n=18
Drahos, 2015[34]	EAC (risk)	International BEACON Consortium	NA	8 case-control	NA	<u>Overweight *vs.* Normal weight</u> All age groups – OR=1.58 (1.37-1.82) ACCORDING TO AGE GROUP < 50 years – OR=1.64 (0.99-2.73) 50-59 years – OR=1.61 (1.18-2.20) 60-69 years – OR=1.93 (1.51-2.46) ≥ 70 years – OR=1.19 (0.93-1.52) <u>Obese *vs.* Normal weight</u> All age groups – OR=2.83 (2.36-3.40) ACCORDING TO AGE GROUP < 50 years – OR=4.19 (2.23-7.87) 50-59 years – OR=2.64 (1.81-3.84) 60-69 years – OR=2.73 (1.99-3.74) ≥ 70 years – OR=2.81 (2.00-3.94)
Fahey, 2015[28]	ESCC, EAC (mortality)	MEDLINE (inception-2014), EMBASE (inception-2014) Citation tracking	("Esophagus"[Mesh] OR "Esophagus"[Title/Abstract] OR "Oesophagus"[Title/Abstract] OR "Esophageal"[Title/Abstract] OR "Oesophageal"[Title/Abstract]) AND ("Neoplasms"[Mesh] OR "Neoplasm"[Title/Abstract] OR "Cancer*"[Title/Abstract] OR "Carcinoma"[Title/Abstract] OR "Adenocarcinoma"[Title/Abstract]) AND (("Survival"	5	JAMA	<u>Overweight/obese *vs.* Normal weight</u> *ESCC* HR=0.80 (0.67-0.95), n=4, I^2=64.9% *EAC* HR=0.80 (0.68-0.95), n=3, I^2=52.1%

			[Mesh]) OR ("Prognosis" [Mesh]) OR ("survival" [Title/Abstract]) OR ("prognosis" [Title/Abstract]) OR ("prognostic" [Title/Abstract])) AND (("smoking" [Title/Abstract]) OR ("tobacco" [Title/Abstract]) OR ("alcohol" [Title/Abstract]) OR ("physical activity" [Title/Abstract]) OR ("exercise" [Title/Abstract]) OR ("sedentary lifestyle"[Title/Abstract]) OR ("body mass index"[Title/Abstract]) OR ("BMI" [Title/Abstract]) OR ("obesity" [Title/Abstract]) OR ("Aspirin"[Title/Abstract]) OR ("Non-Steroidal Anti-Inflammatory"[Title/Abstract]) OR ("NSAID"[Title/Abstract]) OR ("health behavior"[Title/Abstract]) OR ("health behaviour"[Title/Abstract]) OR ("life style"[Title/Abstract]) OR ("lifestyle"[Title/Abstract]) OR ("life-style"[Title/Abstract]) OR ("Smoking"[Mesh]) OR ("Alcohol Drinking"[Mesh]) OR ("Motor Activity"[Mesh]) OR ("Exercise"[Mesh]) OR ("Sedentary Lifestyle"[Mesh]) OR ("Body Mass Index"[Mesh]) OR ("Obesity"[Mesh]) OR ("Health Behavior"[Mesh]) OR ("Life Style"[Mesh]) OR ("Aspirin"[Mesh]) OR ("Anti-Inflammatory Agents, Non-Steroidal"[Mesh])) Restricted to studies published in English			<u>Obese *vs.* Normal weight</u> *ESCC* HR=1.05 (0.76-1.46), n=4, I^2=0.0% *EAC* HR=0.85 (0.68-1.06), n=3, I^2=22.7%
PHYSICAL ACTIVITY						
Behrens, 2014[67]	EC, ESCC, EAC (incidence or mortality)	MEDLINE (inception-2013), ISI Web of Knowledge (inception-2013) Citation tracking	*search strategy included the terms physical activity, exercise, cardiorespiratory fitness, cardiovascular fitness, lifestyle, stomach cancer, stomach carcinoma, gastric cancer, gastric carcinoma, esophageal cancer, esophageal carcinoma, cancer, risk, incidence, and mortality* Restricted to studies published in English	24 9 cohort 15 case-control	Monninkhof *et al.*	<u>High *vs.* low level of physical activity</u> *EC* All studies – RR=0.79 (0.60-1.02), n=21 ACCORDING TO SEX Men – RR=0.70 (0.58-0.85), n=9 Women – RR=0.43 (0.26-0.71), n=3 ACCORDING TO STUDY DESIGN Cohort – RR=0.84 (0.71-0.99), n=7 Case-control – RR=0.76 (0.51-1.12), n=14 ACCORDING TO STUDY QUALITY Upper tertile – RR=0.78 (0.63-0.97), n=7 Intermediate tertile – RR=0.90 (0.42-1.93), n=6 Lower tertile – RR=0.73 (0.61-0.87), n=8

						ACCORDING TO GEOGRAPHIC AREA North America – RR=0.77 (0.64-0.92), n=8 Europe – RR=0.82 (0.54-1.24), n=4 Australia – RR=0.72 (0.57-0.91), n=2 Middle East – RR=0.48 (0.29-0.81), n=3 Asia – RR=1.09 (0.37-3.22), n=4 ACCORDING TO PHYSICAL ACTIVITY DOMAIN Total – RR=0.71 (0.44-1.15), n=3 Recreational – RR=0.72 (0.63-0.83), n=10 Occupational – RR=0.91 (0.46-1.81), n=8 *ESCC* RR=0.94 (0.41-2.16), n=6 *EAC* RR=0.79 (0.66-0.94), n=7
Chen, 2014[68]	EC, ESCC, EAC (risk)	MEDLINE (inception-2013), EMBASE (inception-2013) Citation tracking	*Core search consisted of terms related to physical activity (''exercise,'' ''physical activity,'' ''walking,'' and ''motor activity,'') These were combined with specific terms for cancer sites of interest (''stomach,'' ''gastric,'' ''cardia,'' ''esophagus,'' and ''esophageal'') and with descriptions of cancer (''cancer,'' ''neoplasm,'' and ''carcinoma'')* No language restrictions	8 3 cohort 5 case-control	Methodological quality was assessed using three study components that might affect the strength of the association between physical activity and the risk of esophageal cancer risk: study design; measurement of physical activity; and adjustment for confounding effects	<u>Most physically active *vs.* least active people</u> *EC* All studies – RR=0.73 (0.56-0.97), n=8, I^2=58.4% ACCORDING TO SEX Men – RR=0.81 (0.64-1.02), n=3, I^2=26.8% Women – RR=0.35 (0.04-3.15), n=1 ACCORDING TO STUDY DESIGN Cohort – RR=0.78 (0.66-0.92), n=3, I^2=0.0% Case-control – RR=0.55 (0.28-1.10), n=5, I^2=73.4% ACCORDING TO STUDY QUALITY Low risk of bias – RR=0.79 (0.58-1.08), n=3, I^2=0.0% High risk of bias – RR=0.68 (0.46-1.02), n=5, I^2=74.8% ACCORDING TO STUDY POPULATION Europe and America – RR=0.75 (0.62-0.90), n=6, I^2=2.3% Asia – RR=0.23 (0.01-3.62), n=2, I^2=91.3% *ESCC* RR=0.25 (0.01-4.97), n=2, I^2=92.0%

						EAC RR=0.79 (0.58-1.08), n=2, I^2=0.0%
Schmid, 2014[69]	EC (risk)	COCHRANE (inception-2014), EMBASE (inception-2014), MEDLINE (inception-2014), SCISEARCH (inception-2014) Citation tracking	*Our search included the following terms for sedentary behavior: television (viewing, watching, usage, time, consumption), TV (viewing, watching, usage, time, consumption), video/video game (viewing, watching, usage, time, consumption), computer game (viewing, watching, usage, time, consumption), viewing time, screen time, sedentary (job, time, behavior, lifestyle), sitting (time, hours, behavior, occupational, office, prolonged), and physical inactivity. The search included the following terms for cancer: cancer, neoplasm, carcinoma, adenocarcinoma, tumor, leukemia, and lymphoma. We also searched for terms related to physical activity (eg, physical activity, motor activity, exercise) because several investigations of sedentary behavior were conducted within the context of physical activity studies.* No language restrictions.	3 2 cohort 1 case-control	Newcastle-Ottawa scale	<u>Sedentary behaviour</u> RR=0.87 (0.57-1.34), n=3, I^2=34.1%
Singh, 2014[70]	EC, ESCC, EAC (risk)	MEDLINE (1966-2013), EMBASE (1988-2013), ISI WEB OF KNOWLEDGE (1993-2013) Citation tracking	*A combination of key words was used in the search: (exercise OR physical activity OR walking OR motor activity) AND (esophagus) AND (cancer OR neoplasm OR carcinoma).* No language restrictions.	10 4 cohort 6 case-control	Boyle *et al.*	<u>Most physically active *vs.* least active people</u> *EC* All studies – OR=0.71 (0.57-0.89), n=9, I^2=47% ACCORDING TO STUDY DESIGN Cohort – OR=0.84 (0.71-1.00), n=4, I^2=0% Case-control – OR=0.59 (0.40-0.88), n=5, I^2=51% ACCORDING TO STUDY QUALITY Low quality – OR=0.59 (0.40-0.88), n=5, I^2=51% High quality – OR=0.84 (0.71-1.00), n=4, I^2=0% ACCORDING TO STUDY LOCATION Western – OR=0.72 (0.58-0.89), n=7, I^2=18% Asian – OR=0.43 (0.09-2.00), n=2, I^2=84% *ESCC* OR=1.10 (0.21-5.64), n=3, I^2=95% *EAC* OR=0.68 (0.55-0.85), n=4, I^2=0%
Fahey, 2015[28]	ESCC, EAC (mortality)	MEDLINE	*("Esophagus"[Mesh] OR "Esophagus"[Title/Abstract] OR "Oesophagus"[Title/Abstract] OR*	2	JAMA	<u>Highest *vs.* lowest exercise category</u>

		(inception-2014), EMBASE (inception-2014) Citation tracking	*"Esophageal"[Title/Abstract] OR "Oesophageal"[Title/Abstract]) AND ("Neoplasms"[Mesh] OR "Neoplasm"[Title/Abstract] OR "Cancer*"[Title/Abstract] OR "Carcinoma"[Title/Abstract] OR "Adenocarcinoma"[Title/Abstract]) AND (("Survival" [Mesh]) OR ("Prognosis" [Mesh]) OR ("survival" [Title/Abstract]) OR ("prognosis" [Title/Abstract]) OR ("prognostic" [Title/Abstract])) AND (("smoking" [Title/Abstract]) OR ("tobacco" [Title/Abstract]) OR ("alcohol" [Title/Abstract]) OR ("physical activity" [Title/Abstract]) OR ("exercise" [Title/Abstract]) OR ("sedentary lifestyle"[Title/Abstract]) OR ("body mass index"[Title/Abstract]) OR ("BMI" [Title/Abstract]) OR ("obesity" [Title/Abstract]) OR ("Aspirin"[Title/Abstract]) OR ("Non-Steroidal Anti-Inflammatory"[Title/Abstract]) OR ("NSAID"[Title/Abstract]) OR ("health behavior"[Title/Abstract]) OR ("health behaviour"[Title/Abstract]) OR ("life style"[Title/Abstract]) OR ("lifestyle"[Title/Abstract]) OR ("life-style"[Title/Abstract]) OR ("Smoking"[Mesh]) OR ("Alcohol Drinking"[Mesh]) OR ("Motor Activity"[Mesh]) OR ("Exercise"[Mesh]) OR ("Sedentary Lifestyle"[Mesh]) OR ("Body Mass Index"[Mesh]) OR ("Obesity"[Mesh]) OR ("Health Behavior"[Mesh]) OR ("Life Style"[Mesh]) OR ("Aspirin"[Mesh]) OR ("Anti-Inflammatory Agents, Non-Steroidal"[Mesh]))* Restricted to studies published in English			*EAC* HR=1.20 (0.91-1.58), n=2 *ESCC* HR=0.80 (0.41-1.55), n=1
DIETARY PATTERNS						
Liu, 2014[74]	ESCC (risk)	MEDLINE (inception-2013), EMBASE (inception-2013), CNKI (inception-2013), VJIP (inception-2013) Citation tracking	*Key words used for the literature search included 'oesophageal cancer', 'oesophageal squamous cell carcinoma', 'oesophageal neoplasm', 'dietary pattern', 'nutrient pattern', 'food pattern', 'eating pattern', 'dietary habits', 'diet', 'dietary', and 'nutrients'* Restricted to studies published in English or Chinese	9 case-control	Newcastle-Ottawa scale	<u>Western pattern</u> OR=1.29 (0.83-1.75), n=9, I^2=51.60% Egger test: p=0.853 <u>Healthy pattern</u> OR=0.36 (0.23-0.49), n=9, I^2=67.30% Egger test: p=0.071 <u>Drinker/alcohol pattern</u> OR=2.34 (1.22-3.45), n=4, I^2=48.70% Egger test: p=0.093

GLYCEMIC INDEX/LOAD						
Mulholland, 2009[71]	ESCC (risk)	MEDLINE, EMBASE (inception-2008) Citation tracking	*1) glyc(a)emic index, glyc(a)emic load, blood glucose, blood sugar(s); 2) diet, nutrition, dietary carbohydrate(s), carbohydrate(s), dietary fiber/fiber, fiber/fiber, dietary sugar(s), and dietary sucrose; and 3) cancer, neoplasm(s), neoplasia, adenoma, adenocarcinoma, or carcinoma* No language restrictions	1 case-control	No	<u>Per each 10-unit/d increase in GI intake</u> OR=1.1 (0.9-1.5), n=1 <u>Per each 100-unit/d increment in GL intake</u> OR=1.2 (1.0-1.5), n=1
Turati, 2015[72]	ESCC (risk)	MEDLINE (inception-2015) Citation tracking	*((cancer) OR (neoplasm) OR (carcinoma)) AND((glycemic index)OR (glycemic load) OR (glycaemic index) OR (glycaemic load))* No language restrictions	4 1 cohort 3 case-control	No	<u>Highest *vs.* lowest category of GI intake</u> RR=1.46 (0.90-2.38), n=4, I^2=83.4% <u>Highest *vs.* lowest category of GL intake</u> RR=1.25 (0.45-3.48), n=4, I^2=95.1%
ENERGY INTAKE						
Yu, 2012[73]	EC (risk)	MEDLINE (1966-2012), EMBASE (1985-2012), SCIE (1945-2012) Citation tracking	*energy intake combined with digestive system neoplasms* Restricted to studies published in English	Not specified for EC	No	<u>Highest *vs.* lowest category of energy intake</u> RR=0.96 (0.86-1.07)
MEAT						
Castellsagué, 2000a[78]	ESCC (risk)	Pooled analysis of hospital-based case-control studies conducted in high-risk areas in South America	NA	5 case-control	NA	<u>Almost daily/daily *vs.* never/1-3 per week</u> *Overall* – OR=1.28 (1.02-1.61) *Men* – OR=1.46 (1.11-1.92) *Women* – OR=0.98 (0.62-1.53)
Choi, 2013[92]	EC, ESCC, EAC (risk)	MEDLINE, EMBASE (inception-2012) Citation tracking	*"oesophageal or esophageal or esophagus or oesophagus" and "cancer or neoplasm or carcinoma" and "cohort or prospective or case-control" and "food or diet or meat"* Restricted to studies published in English	27 4 cohort 23 case-control	Newcastle-Ottawa scale	<u>Highest *vs.* lowest red meat intake</u> All studies – RR=1.38 (1.17-1.64), n=22, I^2=67.1% ACCORDING TO SEX Men – RR=1.26 (0.66-2.41), n=3 Women – RR=1.31 (0.78-2.21), n=2 Both – RR=1.42 (1.17-1.71), n=19 ACCORDING TO STUDY DESIGN Cohort – RR=1.26 (1.00-1.59), n=4, I^2=35.3%, Egger test: p=0.79 Case-control – RR=1.44 (1.16-1.80), n=18, I^2=72.8%, Egger test: p=0.34

ACCORDING TO TUMOR TYPE
EAC – RR=1.42 (1.02-1.98), n=9
ESCC – RR=1.55 (1.10-2.17), n=9

ACCORDING TO GEOGRAPHIC AREA
Asia – RR=1.33 (1.09-1.62), n=6
Europe – RR=1.33 (0.86-2.07), n=6
USA – RR=1.32 (1.03-1.70), n=7
South America – RR=2.20 (0.48-10.04), n=3

ACCORDING TO STUDY QUALITY
≥7– RR=1.60 (1.20-2.13), n=8
<7 – RR=1.25 (1.02-1.54), n=14

Highest *vs.* lowest processed meat intake
All studies – RR=1.32 (1.08-1.62), n=18, I^2=58.4%

ACCORDING TO SEX
Men – RR=1.24 (0.58-2.65), n=2
Women – RR=0.61 (0.33-1.13), n=1
Both – RR=1.43 (1.15-1.77), n=16

ACCORDING TO STUDY DESIGN
Cohort – RR=1.25 (0.83-1.86), n=3, I^2=63.4%, Egger test: p=0.65
Case-control – RR=1.36 (1.07-1.74), n=15, I^2=57.1%, Egger test: p=0.80

ACCORDING TO TUMOR TYPE
EAC – RR=1.38 (1.07-1.78), n=8
ESCC – RR=1.08 (0.80-1.44), n=7

ACCORDING TO GEOGRAPHIC AREA
Asia – RR=1.09 (0.61-1.95), n=5
Europe – RR=1.49 (0.99-2.23), n=7
USA – RR=1.30 (1.08-1.57), n=5
South America – RR=0.76 (0.51-1.13), n=1

ACCORDING TO STUDY QUALITY
≥7– RR=1.20 (0.88-1.62), n=6
<7 – RR=1.43 (1.11-1.86), n=12

						Per 100 g/d increment in processed meat intake Cohort – RR=1.37 (0.88-2.13), n=3, I^2=33.5%
Huang, 2013[99]	EAC (risk)	MEDLINE (1966-2012), EMBASE (1974-2012) Citation tracking	*[esophag* AND (adenocarcinomaORcarcinomaORcancer)] combined with ''red meat OR processed meat OR preserved meat OR beef OR pork OR veal OR mutton OR lamb OR ham OR sausage OR bacon OR salted meat''; a similar search was done using the word ''oesophag*,'' a common British spelling for esophagus* Restricted to studies published in English	10 3 cohort 7 case-control	No	<u>Highest *vs.* lowest red meat intake</u> All studies – RR=1.31 (1.05-1.64), n=9, I^2=18.9%, Egger test: p=0.161 ACCORDING TO STUDY DESIGN Cohort – RR=1.12 (0.88-1.41), n=3, I^2=0.0% Case-control – RR=1.56 (1.14-2.14), n=6, I^2=8.1% Population-based – RR=1.50 (1.07-2.11), n=5, I^2=14.0% Hospital-based – RR=2.40 (0.87-6.50), n=1 ACCORDING TO GEOGRAPHIC AREA Europe – RR=1.60 (0.77-3.29), n=3, I^2=71.5% USA – RR=1.26 (1.01-1.58), n=6, I^2=0.0% <u>Increase in red meat intake of 100 g/day</u> RR=1.45 (1.09-1.93), n=7, I^2=61.8% <u>Highest *vs.* lowest processed meat intake</u> All studies – RR=1.41 (1.09-1.83), n=9, I^2=39.4%, Egger test: p=0.359 ACCORDING TO STUDY DESIGN Cohort – RR=1.35 (0.78-2.33), n=3, I^2=75.9% Case-control – RR=1.54 (1.15-2.07), n=6, I^2=0.0% Population-based – RR=1.44 (1.06-1.97), n=5, I^2=0.0% Hospital-based – RR=2.80 (1.09-7.16), n=1 ACCORDING TO GEOGRAPHIC AREA Europe – RR=1.58 (0.75-3.35), n=3, I^2=74.8% USA – RR=1.29 (1.03-1.62), n=6, I^2=5.0% <u>Increase in processed meat intake of 50 g/day</u> RR=1.37 (1.03-1.81), n=7, I^2=71.0%
Qu, 2013[93]	ESCC (risk)	MEDLINE (1966-2012), EMBASE (1974-2012)	*(o)esophageal OR (o)esophagus; cancer OR carcinoma OR neoplasia; and red meat OR processed meat OR preserved meat OR beef OR pork OR veal OR mutton OR lamb OR ham OR sausage OR bacon OR salted meat*	21 2 cohort 19 case-control	No	<u>Highest *vs.* lowest red meat intake</u> All studies – RR=1.57 (1.26-1.95), n=16, I^2=56.0% Only ESCC – RR=1.42 (1.14-1.75), n=7, I^2=6.6%

		Citation tracking	No language restrictions			ACCORDING TO STUDY DESIGN Cohort – RR=1.52 (1.03-2.25), n=2, I^2=0.0% Case-control – RR=1.59 (1.24-2.04), n=14, I^2=60.6% Population-based – RR=1.11 (0.93-1.33), n=2, I^2=0.0% Hospital-based – RR=1.78 (1.35-2.35), n=12, I^2=48.8% ACCORDING TO GEOGRAPHIC AREA Europe – RR=1.50 (0.95-2.38), n=5, I^2=46.7% USA – RR=1.52 (1.01-2.57), n=3, I^2=53.2% South America – RR=2.57 (1.49-4.42), n=3, I^2=52.5% Asia – RR=1.20 (1.03-1.39), n=5, I^2=0.0% <u>Increase in red meat intake of 100 g/day</u> RR=1.41 (1.16-1.70), n=11, I^2=51.7% <u>Highest *vs.* lowest processed meat intake</u> All studies – RR=1.55 (1.22-1.97), n=15, I^2=45.3% Only ESCC – RR=1.41 (1.11-1.78), n=8, I^2=0.0% ACCORDING TO STUDY DESIGN Cohort – RR=1.28 (0.88-1.86), n=2, I^2=0.0% Case-control – RR=1.62 (1.22-2.16), n=13, I^2=51.0% Population-based – RR=1.97 (1.24-3.12), n=4, I^2=25.2% Hospital-based – RR=1.51 (1.05-2.15), n=9, I^2=57.9% ACCORDING TO GEOGRAPHIC AREA Europe – RR=1.73 (0.97-3.08), n=5, I^2=69.6% USA – RR=1.57 (1.05-2.34), n=2, I^2=17.0% South America – RR=1.73 (1.21-2.48), n=2, I^2=0.0% Asia – RR=1.43 (1.01-2.14), n=6, I^2=47.3% <u>Increase in processed meat intake of 50 g/day</u> RR=1.81 (1.32-2.48), n=13, I^2=56.5%
Salehi, 2013[82]	EC, ESCC, EAC (risk)	MEDLINE, EMBASE, WEB OF SCIENCE (1990-2011) Citation tracking	*"meat" or "foods" or "diet" combined with "esophageal cancer," "esophageal neoplasm," "esophagus cancer," or "esophagus neoplasm"; the search was repeated using British spelling* Restricted to studies published in English	35 4 cohort 31 case-control	Critical Appraisal Skills Programme (CASP)	<u>Highest *vs.* lowest total meat intake</u> All studies – RR=0.99 (0.85-1.15), n=21, I^2=49.7%, Egger test: p=0.40 ACCORDING TO STUDY DESIGN Cohort – RR=0.90 (0.59-1.38), n=3

	Population-based case-control – RR=1.33 (0.99-1.81), n=8 Hospital-based case-control – RR=0.95 (0.79-1.14), n=10 ACCORDING TO TUMOR TYPE EAC – RR=1.09 (0.92-1.29), n=6 ESCC – RR=0.89 (0.69-1.14), n=8 ACCORDING TO GEOGRAPHIC AREA Asian – RR=0.77 (0.67-0.88), n=9 European – RR=1.02 (0.77-1.34), n=7 American – RR=1.16 (0.98-1.36), n=5 <u>Increase in total meat intake of 100 g/day</u> RR=1.01 (0.99-1.01), n=9, I^2=33.8% <u>Highest *vs.* lowest red meat intake</u> All studies – RR=1.40 (1.09-1.81), n=14, Egger test: p=0.15 ACCORDING TO STUDY DESIGN Cohort – RR=1.32 (1.03-1.71), n=2 Population-based case-control – RR=1.17 (0.87-1.58), n=5, I^2=0.0% Hospital-based case-control – RR=1.66 (1.02-2.69), n=7, I^2=82.0% ACCORDING TO TUMOR TYPE EAC – RR=1.19 (0.98-1.44), n=6 ESCC – RR=1.63 (1.00-2.63), n=7, I^2=79.0% ACCORDING TO GEOGRAPHIC AREA European – RR=1.57 (1.03-2.38), n=5 American – RR=1.34 (0.97-1.85), n=9 <u>Highest *vs.* lowest processed meat intake</u> All studies – RR=1.41 (1.13-1.76), n=17, I^2=62.0%, Egger test: p=0.75 ACCORDING TO STUDY DESIGN

	Cohort – RR=1.87 (0.62-5.64), n=2 Population-based case-control – RR=1.32 (1.01-1.72), n=7, I^2=0.0% Hospital-based case-control – RR=1.43 (0.99-2.06), n=8, I^2=62.0% ACCORDING TO TUMOR TYPE EAC – RR=1.37 (1.05-1.78), n=6 ESCC – RR=1.17 (0.90-1.51), n=6 ACCORDING TO GEOGRAPHIC AREA Asian – RR=0.78 (0.51-1.19), n=3 European – RR=1.86 (1.20-2.90), n=6 American – RR=1.43 (1.09-1.89), n=8 <u>Increase in processed meat intake of 50 g/day</u> RR=1.57 (1.22-2.01), n=8 <u>Highest *vs.* lowest barbecued meat intake</u> All studies – RR=1.68 (0.88-3.21), n=3 ACCORDING TO STUDY DESIGN Population-based case-control – RR=0.99 (0.62-1.59), n=1 Hospital-based case-control – RR=2.37 (1.41-3.98), n=2 <u>Highest *vs.* lowest white meat intake</u> All studies – RR=0.71 (0.59-0.86), n=4, I^2=6.0% ACCORDING TO STUDY DESIGN Cohort – RR=0.80 (0.63-1.00), n=1 Population-based case-control – RR=0.51 (0.23-1.13), n=1 Hospital-based case-control – RR=0.64 (0.48-0.85), n=2 <u>Highest *vs.* lowest poultry meat intake</u> All studies – RR=0.87 (0.60-1.24), n=9, Egger test: p=0.81

						ACCORDING TO STUDY DESIGN Cohort – RR=1.93 (0.99-3.76), n=1 Population-based case-control – RR=0.88 (0.65-1.19), n=4 Hospital-based case-control – RR=0.68 (0.35-1.30), n=4 ACCORDING TO TUMOR TYPE EAC – RR=1.02 (0.52-2.00), n=3 ESCC – RR=0.66 (0.31-1.40), n=3 ACCORDING TO GEOGRAPHIC AREA Asian – RR=1.42 (0.62-3.25), n=1 European – RR=0.74 (0.34-1.74), n=4 American – RR=0.89 (0.64-1.24), n=4
Zhu, 2014[83]	EC, ESCC, EAC (risk)	MEDLINE (inception-2013), EMBASE (inception-2013), COCHRANE (inception-2013) Citation tracking	*The search strategy included terms of outcome (esophageal cancer, oesophageal cancer, esophageal neoplasms, esophageal squamous cell carcinoma, and esophageal adenocarcinoma) and exposure (meat, red meat, processed meat, white meat, poultry, fish, beef, pork, lamb, and goat).* No language restrictions	35 7 cohort 28 case-control	Newcastle-Ottawa scale	*EC* <u>Highest *vs.* lowest total meat intake</u> All studies – RR=1.19 (0.98-1.46), n=24, I^2=73.3%, Egger test: p=0.009; Begg test: p=0.107 High-quality studies – RR=1.26 (0.98-1.63), n=16, I^2=77.8% ACCORDING TO STUDY DESIGN Cohort – RR=0.94 (0.67-1.32), n=4, I^2=60.5% Case-control – RR=1.24 (0.99-1.57), n=20, I^2=70.7% Population-based case-control – RR=1.54 (1.13-2.10), n=10, I^2=76.1% Hospital-based case-control – RR=0.87 (0.73-1.04), n=11, I^2=17.3% ACCORDING TO GEOGRAPHIC AREA Asia – RR=0.92 (0.75-1.12), n=11, I^2=50.4% Europe – RR=0.93 (0.73-1.18), n=6, I^2=49.2% USA – RR=1.85 (0.89-3.85), n=4, I^2=79.9% South America – RR=0.87 (0.47-1.63), n=2, I^2=0.0% Australia – RR=2.19 (1.66-2.90), n=1 <u>Highest *vs.* lowest red meat intake</u> All studies – RR=1.55 (1.22-1.96), n=15, I^2=63.6%, Egger test: p=0.326; Begg test: p=0.132

High-quality studies – RR=1.52 (1.15-2.02), n=12, I^2=68.5%

ACCORDING TO STUDY DESIGN
Cohort – RR=1.21 (0.98-1.50), n=3, I^2=40.9%
Case-control – RR=1.78 (1.30-2.44), n=12, I^2=68.3%
Population-based case-control – RR=1.42 (1.02-1.98), n=4, I^2=0.0%
Hospital-based case-control – RR=2.01 (1.28-3.16), n=8, I^2=78.5%

ACCORDING TO GEOGRAPHIC AREA
Asia – RR=1.42 (1.07-1.87), n=2, I^2=0.0%
Europe – RR=1.32 (0.93-1.87), n=6, I^2=52.1%
USA – RR=1.36 (1.09-1.68), n=4, I^2=0.0%
South America – RR=2.64 (0.88-7.89), n=3, I^2=84.6%

Highest *vs.* lowest processed meat intake
All studies – RR=1.33 (1.04-1.69), n=15, I^2=61.5%, Egger test: p=0.159; Begg test: p=0.345

High-quality studies – RR=1.35 (1.03-1.78), n=12, I^2=66.9%

ACCORDING TO STUDY DESIGN
Cohort – RR=1.25 (0.83-1.86), n=3, I^2=63.4%
Case-control – RR=1.29 (1.00-1.93), n=12, I^2=63.4%
Population-based case-control – RR=1.37 (1.00-1.88), n=5, I^2=0.0%
Hospital-based case-control – RR=1.44 (0.84-2.50), n=7, I^2=78.7%

ACCORDING TO GEOGRAPHIC AREA
Asia – RR=1.00 (0.52-1.94), n=2, I^2=0.0%
Europe – RR=1.57 (0.95-2.58), n=6, I^2=72.6%
USA – RR=1.23 (1.00-1.50), n=4, I^2=0.0%
South America – RR=1.07 (0.48-2.41), n=3, I^2=80.0%

Highest *vs.* lowest white meat intake
All studies – RR=0.72 (0.60-0.86), n=4, I^2=0.0%, Egger test: p=0.332; Begg test: p=0.624

	ACCORDING TO STUDY DESIGN Cohort – RR=0.80 (0.64-1.00), n=1 Case-control – RR=0.58 (0.42-0.80), n=3, I^2=0.0% ACCORDING TO GEOGRAPHIC AREA Europe – RR=0.51 (0.23-1.13), n=1 USA – RR=0.80 (0.64-1.00), n=1 South America – RR=0.60 (0.42-0.84), n=2, I^2=0.0% <u>Highest *vs.* lowest poultry intake</u> All studies – RR=0.83 (0.72-0.96), n=12, I^2=34.5%, Egger test: p=0.858; Begg test: p=0.956 High-quality studies – RR=0.78 (0.57-1.07), n=7, I^2=57.3% ACCORDING TO STUDY DESIGN Cohort – RR=1.02 (0.64-1.62), n=2, I^2=66.2% Case-control – RR=0.76 (0.63-0.91), n=10, I^2=11.4% Population-based case-control – RR=0.83 (0.66-1.04), n=5, I^2=0.0% Hospital-based case-control – RR=0.64 (0.46-0.88), n=6, I^2=6.7% ACCORDING TO GEOGRAPHIC AREA Asia – RR=0.85 (0.67-1.08), n=5, I^2=0.0% Europe – RR=0.77 (0.34-1.74), n=4, I^2=76.7% USA – RR=0.87 (0.70-1.07), n=3, I^2=0.0% *ESCC* <u>Highest *vs.* lowest total meat intake</u> All studies – RR=0.92 (0.75-1.14), n=18, I^2=68.5% High-quality studies – RR=0.87 (0.67-1.14), n=12, I^2=72.0% ACCORDING TO STUDY DESIGN Cohort – RR=0.65 (0.49-0.87), n=3, I^2=64.8% Case-control – RR=1.05 (0.79-1.39), n=14, I^2=66.2% Population-based case-control – RR=1.27 (0.80-2.00), n=7, I^2=75.6%

	Hospital-based case-control – RR=0.83 (0.68-1.01), n=8, I^2=21.1% ACCORDING TO GEOGRAPHIC AREA Asia – RR=0.92 (0.75-1.12), n=11, I^2=50.4% Europe – RR=0.74 (0.55-0.99), n=3, I^2=2.5% USA – RR=2.01 (0.82-4.95), n=1 South America – RR=0.87 (0.47-1.63), n=2, I^2=0.0% Australia – RR=2.84 (1.67-4.83), n=1 <u>Highest *vs.* lowest red meat intake</u> All studies – RR=1.86 (1.31-2.66), n=10, I^2=72.6%, Egger test: p=0.415; Begg test: p=0.621 High-quality studies – RR=1.93 (1.23-3.03), n=8, I^2=76.2% ACCORDING TO STUDY DESIGN Cohort – RR=1.54 (1.04-2.27), n=2, I^2=47.0% Case-control – RR=2.01 (1.28-3.16), n=8, I^2=78.5% ACCORDING TO GEOGRAPHIC AREA Asia – RR=1.42 (1.07-1.87), n=2, I^2=0.0% Europe – RR=1.87 (1.04-3.36), n=4, I^2=66.3% USA – RR=1.79 (1.07-3.01), n=1 South America – RR=2.64 (0.88-7.89), n=3, I^2=84.6% <u>Highest *vs.* lowest processed meat intake</u> All studies – RR=1.35 (0.92-2.00), n=10, I^2=71.3% High-quality studies – RR=1.44 (0.92-2.26), n=8, I^2=76.8% ACCORDING TO STUDY DESIGN Cohort – RR=1.34 (0.62-2.92), n=2, I^2=68.5% Case-control – RR=1.37 (0.84-2.24), n=8, I^2=75.4% Population-based case-control – RR=0.93 (0.38-2.29), n=1 Hospital-based case-control – RR=1.44 (0.84-2.50), n=7, I^2=78.7% ACCORDING TO GEOGRAPHIC AREA Asia – RR=1.00 (0.52-1.94), n=2, I^2=0.0%

Europe – RR=1.84 (0.86-3.97), n=4, I^2=79.4%
USA – RR=1.32 (0.83-2.10), n=1
South America – RR=1.07 (0.48-2.41), n=3, I^2=80.0%

Highest *vs.* lowest white meat intake
All studies – RR=0.63 (0.48-0.83), n=3, I^2=0.0%,
Egger test: p=0.420; Begg test: p=0.117

ACCORDING TO STUDY DESIGN
Cohort – RR=0.69 (0.44-1.08), n=1
Case-control – RR=0.60 (0.42-0.84), n=2, I^2=0.0%

ACCORDING TO GEOGRAPHIC AREA
USA – RR=0.69 (0.44-1.08), n=1
South America – RR=0.60 (0.42-0.84), n=2, I^2=0.0%

Highest *vs.* lowest poultry intake
All studies – RR=0.73 (0.60-0.89), n=9, I^2=6.9%,
Egger test: p=0.285; Begg test: p=0.421

High-quality studies – RR=0.56 (0.40-0.77), n=4, I^2=0.0%

ACCORDING TO STUDY DESIGN
Cohort – RR=0.69 (0.42-1.13), n=1
Case-control – RR=0.74 (0.60-0.91), n=8, I^2=16.8%
Population-based case-control – RR=0.83 (0.63-1.09), n=3, I^2=8.2%
Hospital-based case-control – RR=0.64 (0.46-0.88), n=6, I^2=6.7%

ACCORDING TO GEOGRAPHIC AREA
Asia – RR=0.85 (0.67-1.08), n=5, I^2=0.0%
Europe – RR=0.47 (0.31-0.73), n=3, I^2=0.0%
USA – RR=0.69 (0.42-1.13), n=1

EAC

Highest *vs.* lowest total meat intake
All studies – RR=1.96 (1.26-3.03), n=6, I^2=62.9%,
Egger test: p=0.743; Begg test: p=0.851

	High-quality studies – RR=1.96 (1.26-3.03), n=6, I^2=62.9% ACCORDING TO STUDY DESIGN Cohort – RR=1.79 (0.86-3.75), n=1 Case-control – RR=1.99 (1.18-3.36), n=5, I^2=70.2% ACCORDING TO GEOGRAPHIC AREA Europe – RR=1.54 (0.91-2.60), n=2, I^2=0.0% USA – RR=2.24 (0.84-6.00), n=3, I^2=83.7% Australia – RR=2.12 (1.30-3.46), n=1 <u>Highest *vs.* lowest red meat intake</u> All studies – RR=1.20 (0.98-1.48), n=7, I^2=1.9% High-quality studies – RR=1.15 (0.93-1.42), n=6, I^2=0.0% ACCORDING TO STUDY DESIGN Cohort – RR=1.09 (0.84-1.41), n=3, I^2=30.0% Case-control – RR=1.42 (1.02-1.98), n=4, I^2=0.0% ACCORDING TO GEOGRAPHIC AREA Europe – RR=1.02 (0.69-1.51), n=3, I^2=26.9% USA – RR=1.28 (1.01-1.62), n=4, I^2=0.0% <u>Highest *vs.* lowest processed meat intake</u> All studies – RR=1.23 (1.01-1.50), n=7, I^2=40.9%, Egger test: p=0.289; Begg test: p=0.186 High-quality studies – RR=1.20 (0.97-1.47), n=6, I^2=44.5% ACCORDING TO STUDY DESIGN Cohort – RR=1.21 (0.67-2.16), n=3, I^2=69.3% Case-control – RR=1.45 (1.04-2.03), n=4, I^2=0.0% ACCORDING TO GEOGRAPHIC AREA Europe – RR=1.31 (0.65-2.65), n=3, I^2=68.0% USA – RR=1.21 (0.96-1.51), n=4, I^2=0.0% <u>Highest *vs.* lowest white meat intake</u> All studies – RR=0.80 (0.63-1.02), n=2, I^2=26.8%

						Highest *vs.* lowest poultry intake All studies – RR=1.01 (0.69-1.46), n=4, I^2=50.5% High-quality studies – RR=1.01 (0.69-1.46), n=4, I^2=50.5% ACCORDING TO STUDY DESIGN Cohort – RR=1.27 (0.64-2.50), n=2, I^2=72.9% Case-control – RR=0.83 (0.55-1.26), n=2, I^2=30.4% ACCORDING TO GEOGRAPHIC AREA Europe – RR=1.93 (0.99-3.76), n=1 USA – RR=0.91 (0.72-1.15), n=3, I^2=0.0%
FISH						
Han, 2013[96]	ESCC, EAC (risk)	MEDLINE, EMBASE (inception-2012) Citation tracking	*(o)esophag*; cancer OR carcinoma OR neoplasia OR adenocarcinoma; fish OR shellfish OR seafood* Restricted to studies published in English	24 3 cohort 21 case-control	No	*EAC* Highest *vs.* lowest fish intake All studies – RR=0.86 (0.61-1.22), n=6, I^2=58.4% ACCORDING TO STUDY DESIGN Cohort – RR=0.78 (0.59-1.03), n=1 Case-control – RR=0.86 (0.53-1.41), n=5, I^2=64.4% Population-based case-control – RR=0.86 (0.53-1.41), n=5, I^2=64.4% ACCORDING TO GEOGRAPHIC AREA Europe – RR=1.32 (0.81-2.14), n=2, I^2=0.0% USA – RR=0.72 (0.48-1.09), n=4, I^2=62.9% *ESCC* Highest *vs.* lowest fish intake All studies – RR=0.81 (0.66-0.99), n=17, I^2=51.9%, Egger test: p=0.773, Begg test: p=0.318 ACCORDING TO STUDY DESIGN Cohort – RR=0.87 (0.60-1.27), n=3, I^2=46.1% Case-control – RR=0.79 (0.62-1.02), n=14, I^2=55.1% Population-based case-control – RR=1.58 (1.09-2.29), n=3, I^2=0.0%

						Hospital-based case-control – RR=0.66 (0.55-0.80), n=11, I^2=12.9% ACCORDING TO GEOGRAPHIC AREA Europe – RR=0.60 (0.42-0.86), n=4, I^2=40.9% USA – RR=1.30 (0.71-2.39), n=2, I^2=59.6% South America – RR=0.74 (0.43-1.28), n=3, I^2=41.6% Asia – RR=0.86 (0.65-1.13), n=8, I^2=43.3% <u>Increase in fish intake of 1 serving/week</u> RR=0.81 (0.73-0.89), n=6, I^2=0.0% <u>Increase in fish intake of 20 g/day</u> RR=0.86 (0.58-1.27), n=3, I^2=88.9%
Salehi, 2013[82]	EC, ESCC, EAC (risk)	MEDLINE, EMBASE, WEB OF SCIENCE (1990-2011) Citation tracking	*"meat" or "foods" or "diet" combined with "esophageal cancer," "esophageal neoplasm," "esophagus cancer," or "esophagus neoplasm"; the search was repeated using British spelling* Restricted to studies published in English	35 4 cohort 31 case-control	Critical Appraisal Skills Programme (CASP)	<u>Highest *vs.* lowest fish intake</u> All studies – RR=0.80 (0.64-1.00), n=17, Egger test: p=0.47 ACCORDING TO STUDY DESIGN Cohort – RR=0.59 (0.36-0.97), n=1 Population-based case-control – RR=1.14 (0.82-1.44), n=7 Hospital-based case-control – RR=0.69 (0.52-0.91), n=9 ACCORDING TO TUMOR TYPE EAC – RR=0.90 (0.52-1.56), n=3 ESCC – RR=0.71 (0.48-1.06), n=6 ACCORDING TO GEOGRAPHIC AREA Asian – RR=0.98 (0.68-1.42), n=6 European – RR=0.66 (0.49-0.88), n=7 American – RR=0.87 (0.44-1.73), n=4 <u>Increase in fish intake of 50 g/day</u> RR=0.62 (0.43-0.87), n=7
Yu, 2014[100]	EC (incidence)	MEDLINE (1966-2013), EMBASE (1985-2013), SCIE (1945-2013)	*Using the Medical Subject Heading terms fish and gastrointestinal neoplasm, or esophageal neoplasm, or stomach neoplasm, or colorectal neoplasm, or hepatocellular neoplasm, or pancreatic neoplasm* Restricted to studies published in English	2 cohort	No	<u>Fish consumers *vs.* non/lowest consumers</u> RR=0.91 (0.83-0.99), n=2

		Citation trackinh				
Zhu, 2014[83]	EC, ESCC, EAC (risk)	MEDLINE (inception-2013), EMBASE (inception-2013), COCHRANE (inception-2013) Citation tracking	*The search strategy included terms of outcome (esophageal cancer, oesophageal cancer, esophageal neoplasms, esophageal squamous cell carcinoma, and esophageal adenocarcinoma) and exposure (meat, red meat, processed meat, white meat, poultry, fish, beef, pork, lamb, and goat).* No language restrictions	25 3 cohort 22 case-control	Newcastle-Ottawa scale	*EC* <u>Highest *vs.* lowest fish intake</u> All studies – RR=0.95 (0.76-1.19), n=25, I^2=79.2%, Egger test: p=0.416; Begg test: p=0.368 High-quality studies – RR=0.96 (0.73-1.25), n=16, I^2=80.2% ACCORDING TO STUDY DESIGN Cohort – RR=0.83 (0.68-1.01), n=3, I^2=23.7% Case-control – RR=0.98 (0.74-1.28), n=22, I^2=81.5% Population-based case-control – RR=1.31 (0.84-2.05), n=10, I^2=87.0% Hospital-based case-control – RR=0.77 (0.58-1.03), n=13, I^2=68.4% ACCORDING TO GEOGRAPHIC AREA Asia – RR=1.18 (0.79-1.76), n=12, I^2=86.4% Europe – RR=0.65 (0.53-0.81), n=7, I^2=41.8% USA – RR=0.91 (0.66-1.26), n=5, I^2=62.0% South America – RR=1.50 (0.60-4.00), n=1 *ESCC* <u>Highest *vs.* lowest fish intake</u> All studies – RR=1.08 (0.80-1.46), n=19, I^2=90.5% High-quality studies – RR=1.15 (0.78-1.69), n=12, I^2=91.4% ACCORDING TO STUDY DESIGN Cohort – RR=1.05 (0.51-2.14), n=3, I^2=92.1% Case-control – RR=1.09 (0.77-1.55), n=16, I^2=84.8% Population-based case-control – RR=1.82 (0.94-3.53), n=7, I^2=90.5% Hospital-based case-control – RR=0.79 (0.55-1.13), n=10, I^2=72.9% ACCORDING TO GEOGRAPHIC AREA Asia – RR=1.18 (0.79-1.76), n=12, I^2=86.4%

						Europe – RR=0.62 (0.47-0.82), n=4, I^2=36.7% USA – RR=1.30 (0.71-2.39), n=2, I^2=59.6% South America – RR=1.50 (0.60-4.00), n=1 *EAC* Highest *vs.* lowest fish intake All studies – RR=0.81 (0.54-1.20), n=5, I^2=63.1% High-quality studies – RR=0.81 (0.54-1.20), n=5, I^2=63.1% ACCORDING TO STUDY DESIGN Cohort – RR=0.78 (0.69-1.03), n=1 Case-control – RR=0.77 (0.42-1.43), n=4, I^2=71.4% ACCORDING TO GEOGRAPHIC AREA Europe – RR=1.49 (0.72-3.10), n=1 USA – RR=0.72 (0.48-1.09), n=4, I^2=62.9%
FRUITS						
Castellsagué, 2000a[78]	ESCC (risk)	Pooled analysis of hospital-based case-control studies conducted in high-risk areas in South America	NA	5 case-control	NA	1-3 per week or month *vs.* never/rarely *Overall* – OR=0.43 (0.31-0.58) *Men* – OR=0.39 (0.27-0.55) *Women* – OR=0.64 (0.28-1.45) Almost daily/daily *vs.* never/rarely *Overall* – OR=0.37 (0.27-0.51) *Men* – OR=0.31 (0.22-0.45) *Women* – OR=0.68 (0.30-1.52)
Riboli, 2003[76]	EC (risk, incidence, mortality)	MEDLINE (1973-2001) Citation tracking	*Not stated* Restricted to studies published in English	13 1 cohort 12 case-control	No	Increase in fruits intake of 100 g/day All studies – RR=0.72 (0.62-0.83), n=15 ACCORDING TO GEOGRAPHIC AREA Europe – RR=0.82 (0.66-1.01), n=4 United Sates – RR=0.80 (0.67-0.96), n=2 Asia – RR=0.68 (0.43-1.06), n=5 South America – RR=0.56 (0.38-0.82), n=4
WCRF, 2007[22]	EC (risk, incidence, mortality)	MEDLINE, WEB OF SCIENCE, CINAHL, BIOSIS,	*Not specifically stated* No language restrictions	8 case-control	No	*Fruits (general)* Per 100 g/d increment RR=0.56 (0.42-0.74), n=8, I^2=78.6% *Citrus fruit*

		CAB Abstracts, LILACS, EMBASE COCHRANE (inception-2006) Citation tracking				<u>Per 50 g/d increment</u> RR=0.70 (0.56-0.88), n=7, I^2=88.1%
Soerjomataram, 2010[77]	EC (risk, incidence, mortality)	Not stated	*Not stated* Restricted to European studies published in English up to December 2008	6 1 cohort 5 case-control	No	<u>Per 1 g/d increment</u> RR=0.995 (0.994-0.997), n=6
Liu, 2013[79]	ESCC (risk)	MEDLINE, EMBASE (inception-2012) Citation tracking	*[esophag* AND (neoplasm OR carcinoma OR cancer)] combined with "nutrition OR diet OR lifestyle OR fruit OR vegetable"; a similar search was done using the word "oesophag*," a common British spelling for esophagus* Restricted to studies published in English	32 5 cohort 27 case-control	No	<u>Highest *vs.* lowest fruits intake</u> All studies – RR=0.53 (0.44-0.64), n=29, I^2=73.7%, Egger test: p=0.128, Begg test: p=0.268 Only ESCC – RR=0.51 (0.40-0.64), n=17, I^2=66.0% ACCORDING TO STUDY DESIGN Cohort – RR=0.68 (0.55-0.86), n=5, I^2=25.1% Case-control – RR=0.51 (0.41-0.63), n=24, I^2=71.5% Population-based case-control – RR=0.73 (0.58-0.92), n=6, I^2=0.0% Hospital-based case-control – RR=0.44 (0.34-0.57), n=18, I^2=74.9% ACCORDING TO GEOGRAPHIC AREA Europe – RR=0.37 (0.22-0.63), n=7, I^2=78.1% USA – RR=0.40 (0.18-0.92), n=3, I^2=66.9% South America – RR=0.41 (0.29-0.56), n=3, I^2=72.9% Asia – RR=0.67 (0.56-0.79), n=16, I^2=49.7% <u>Per 100 g/d increment in fruits intake</u> All studies – RR=0.61 (0.52-0.72), n=18, I^2=89.7% ACCORDING TO STUDY DESIGN Cohort – RR=0.87 (0.82-0.91), n=4, I^2=0.0% Case-control – RR=0.52 (0.40-0.67), n=14, I^2=88.7%
Li, 2014[80]	EAC (risk)	MEDLINE (inception-2013), EMBASE (inception-2013)	*With the following text words and/or Medical Subject Heading (MeSH) terms: (1) "esophag*" OR "oesophag*"; (2) "neoplasm" OR "carcinoma" OR "adenocarcinoma"; (3) "nutrition" OR "diet" OR "dietary" OR "lifestyle" OR "fruit" OR "vegetable"; and (4) "case–control" OR "cohort"*	9 3 cohort 6 case-control	Newcastle-Ottawa scale	<u>High *vs.* low fruit intake</u> All studies – RR=0.73 (0.55-0.98), n=9, I^2=52.9%, Egger test: p=0.062, Begg test: p=0.118 ACCORDING TO STUDY DESIGN Cohort – RR=0.99 (0.72-1.36), n=3, I^2=0.0%

		Citation tracking	Restricted to studies published in English			Case-control – RR=0.59 (0.38-0.90), n=6, I^2=62.6% Population-based case-control – RR=0.61 (0.37-1.02), n=4, I^2=62.6% Hospital-based case-control – RR=0.40 (0.09-1.92), n=2, I^2=81.3% ACCORDING TO GEOGRAPHIC AREA Europe – RR=0.58 (0.36-0.93), n=6, I^2=62.6% USA – RR=0.90 (0.65-1.25), n=2, I^2=0.0% <u>Dose-response analysis</u> Per 100g/day increment – RR=0.87 (0.76-0.99), n=6, I^2=71.0%
VEGETABLES						
Castellsagué, 2000a[78]	ESCC (risk)	Pooled analysis of hospital-based case-control studies conducted in high-risk areas in South America	NA	5 case-control	NA	<u>1-3 per week or month *vs.* never/rarely</u> *Overall* – OR=0.60 (0.43-0.84) *Men* – OR=0.56 (0.39-0.82) *Women* – OR=0.62 (0.28-1.39) <u>Almost daily/daily *vs.* never/rarely</u> *Overall* – OR=0.62 (0.44-0.88) *Men* – OR=0.64 (0.44-0.95) *Women* – OR=0.48 (0.21-1.08)
Riboli, 2003[76]	EC (risk, incidence, mortality)	MEDLINE (1973-2001) Citation tracking	*Not stated* Restricted to studies published in English	13 1 cohort 12 case-control	No	<u>Increase in vegetables intake of 100 g/day</u> All studies – RR=0.89 (0.82-0.97), n=13 ACCORDING TO GEOGRAPHIC AREA Europe – RR=0.79 (0.68-0.92), n=4 United Sates – RR=0.81 (0.67-0.98), n=2 Asia – RR=0.98 (0.91-1.05), n=5 South America – RR=0.68 (0.32-1.43), n=2
WCRF, 2007[22]	EC (risk, incidence, mortality)	MEDLINE, WEB OF SCIENCE, CINAHL, BIOSIS, CAB Abstracts, LILACS, EMBASE COCHRANE (inception-2006) Citation tracking	*Not specifically stated* No language restrictions	5 case-control	No	<u>Per 50 g/d increment</u> Non-starchy vegetables – RR=0.87 (0.72-1.05), n=5, I^2=93.9% Raw vegetables – RR=0.69 (0.58-0.83), n=5, I^2=86.3%

Islami, 2009[81]	ESCC (risk)	MEDLINE, WEB OF SCIENCE, J-EAST, INDMED, VIP, CNKI (inception-2009) Citation tracking	*(oesophageal OR oesophageal OR oesophagus OR oesophagus) AND (cancer OR carcinoma OR adenocarcinoma OR neoplasm OR neoplasia OR neoplastic) AND (pickle OR pickled OR moldy OR fermented)* Restricted to studies published in English or Chinese	34 3 cohort 31 case-control	No	<u>Highest *vs.* lowest pickled vegetables intake</u> All studies – OR=2.08 (1.66-2.60), n=34, I^2=88%, Egger test: p=0.01, Begg test: p=0.30 After excluding the three most influential studies – OR=2.32 (1.92-2.81), n=31, I^2=75% Large studies – OR=2.09 (1.67-2.63), n=30, I^2=89% Adjusted results – OR=2.15 (1.64-2.81), n=24, I^2=88% ACCORDING TO STUDY DESIGN Cohort – OR=1.52 (0.82-1.63), n=3, I^2=81% Case-control – OR=2.18 (1.75-2.73), n=31, I^2=83% Population-based case-control – OR=2.11 (1.56-2.85), n=18, I^2=91%
Soerjomataram, 2010[77]	EC (risk, incidence, mortality)	Not stated	*Not stated* Restricted to European studies published in English up to December 2008	6 1 cohort 5 case-control	No	<u>Per 1 g/d increment</u> RR=0.996 (0.994-0.998), n=6
Liu, 2013[79]	ESCC (risk)	MEDLINE, EMBASE (inception-2012) Citation tracking	*[esophag* AND (neoplasm OR carcinoma OR cancer)] combined with "nutrition OR diet OR lifestyle OR fruit OR vegetable"; a similar search was done using the word "oesophag*," a common British spelling for esophagus* Restricted to studies published in English	32 5 cohort 27 case-control	No	<u>Highest *vs.* lowest vegetables intake</u> All studies – RR=0.56 (0.45-0.69), n=24, I^2=75.8%, Egger test: p=0.832, Begg test: p=0.980 Only ESCC – RR=0.57 (0.43-0.75), n=15, I^2=78.5% ACCORDING TO STUDY DESIGN Cohort – RR=0.80 (0.61-1.07), n=5, I^2=36.2% Case-control – RR=0.52 (0.41-0.65), n=19, I^2=64.6% Population-based case-control – RR=0.57 (0.31-1.05), n=4, I^2=68.8% Hospital-based case-control – RR=0.51 (0.40-0.65), n=15, I^2=66.0% ACCORDING TO GEOGRAPHIC AREA Europe – RR=0.30 (0.15-0.60), n=5, I^2=81.9% USA – RR=0.65 (0.43-0.98), n=3, I^2=0.0% South America – RR=0.68 (0.54-0.87), n=4, I^2=0.0% Asia – RR=0.63 (0.47-0.83), n=12, I^2=74.8% <u>Per 100 g/d increment in vegetables intake</u> All studies – RR=0.84 (0.78-0.92), n=15, I^2=82.0% ACCORDING TO STUDY DESIGN Cohort – RR=0.92 (0.84-1.01), n=4, I^2=82.0%

						Case-control – RR=0.78 (0.69-0.89), n=11, I^2=83.0%
Li, 2014[80]	EAC (risk)	MEDLINE (inception-2013), EMBASE (inception-2013) Citation tracking	*With the following text words and/or Medical Subject Heading (MeSH) terms: (1) "esophag*" OR "oesophag*"; (2) "neoplasm" OR "carcinoma" OR "adenocarcinoma"; (3) "nutrition" OR "diet" OR "dietary" OR "lifestyle" OR "fruit" OR "vegetable"; and (4) "case–control" OR "cohort"* Restricted to studies published in English	9 3 cohort 6 case-control	Newcastle-Ottawa scale	<u>High *vs.* low vegetables intake</u> All studies – RR=0.76 (0.59-0.96), n=9, I^2=40.4%, Egger test: p=0.629, Begg test: p=0.348 ACCORDING TO STUDY DESIGN Cohort – RR=0.76 (0.54-1.05), n=3, I^2=0.0% Case-control – RR=0.75 (0.53-1.06), n=6, I^2=58.5% Population-based case-control – RR=0.71 (0.45-1.11), n=5, I^2=64.7% Hospital-based case-control – RR=0.90 (0.61-1.33), n=1 ACCORDING TO GEOGRAPHIC AREA Europe – RR=0.73 (0.46-1.14), n=5, I^2=52.2% USA – RR=0.82 (0.58-1.14), n=3, I^2=22.0% <u>Dose-response analysis</u> Per 100g/day increment – RR=0.91 (0.83-0.99), n=6, I^2=22.9%
FRUITS AND VEGETABLES						
Lock, 2005[75]	EC (risk)	MEDLINE, EMBASE, COCHRANE (1980-2000) CAB Abstracts (1987-2000) Citation tracking	*"fruit" or "vegetables" and "coronary heart disease", "cerebrovascular disorder", "lung", "colorectal", "stomach" and "esophageal", "neoplasms" and "cancer"; all search terms were linked to MESH headings and exploded* Restricted to studies published in English	32 4 cohort 28 case-control	No	<u>Change per increase of 80 g per day in intake of fruit and vegetables, by age group</u> 15-29 years – RR=0.94 (0.88-1.01) 30-44 years – RR=0.94 (0.88-1.01) 45-59 years – RR=0.94 (0.88-1.01) 60-69 years – RR=0.94 (0.88-1.01) 70-79 years – RR=0.95 (0.89-1.02) ≥ 80 years – RR=0.97 (0.91-1.04)
Li, 2014[80]	EAC (risk)	MEDLINE (inception-2013), EMBASE (inception-2013) Citation tracking	*With the following text words and/or Medical Subject Heading (MeSH) terms: (1) "esophag*" OR "oesophag*"; (2) "neoplasm" OR "carcinoma" OR "adenocarcinoma"; (3) "nutrition" OR "diet" OR "dietary" OR "lifestyle" OR "fruit" OR "vegetable"; and (4) "case–control" OR "cohort"* Restricted to studies published in English	5 1 cohort 4 case-control	Newcastle-Ottawa scale	<u>High *vs.* low fruits and vegetables intake</u> All studies – RR=0.68 (0.49-0.93), n=5, I^2=38.9% ACCORDING TO STUDY DESIGN Cohort – RR=0.99 (0.61-1.61), n=1 Case-control – RR=0.61 (0.44-0.84), n=4, I^2=20.7% Population-based case-control – RR=0.65 (0.49-0.86), n=3, I^2=0.0% Hospital-based case-control – RR=0.25 (0.07-0.86), n=1 ACCORDING TO GEOGRAPHIC AREA Europe – RR=0.54 (0.32-0.82), n=3, I^2=25.1%

						USA – RR=0.99 (0.61-1.61), n=1 <u>Dose-response analysis</u> Per 100g/day increment – RR=0.88 (0.78-0.98), n=4, I^2=84.0%
MILK AND DAIRY PRODUCTS						
WCRF, 2007[22]	EC (risk, incidence, mortality)	MEDLINE, WEB OF SCIENCE, CINAHL, BIOSIS, CAB Abstracts, LILACS, EMBASE COCHRANE (inception-2006) Citation tracking	*Not specifically stated* No language restrictions	5 1 cohort 4 case-control	No	<u>Per 20 g/d increment</u> Cohort – RR=0.90 (0.83-0.98), n=1 Case-control – RR=0.89 (0.78-1.01), n=4, I^2=64.6%
EGGS						
WCRF, 2007[22]	EC (risk, incidence, mortality)	MEDLINE, WEB OF SCIENCE, CINAHL, BIOSIS, CAB Abstracts, LILACS, EMBASE COCHRANE (inception-2006) Citation tracking	*Not specifically stated* No language restrictions	5 1 cohort 4 case-control	No	<u>Per 50 g/d increment</u> Cohort – RR=1.18 (0.96-1.45), n=1 Case-control – RR=1.28 (0.98-1.66), n=4, I^2=82.2%
FAT INTAKE						
Castellsagué, 2000a[78]	ESCC (risk)	Pooled analysis of hospital-based case-control studies conducted in high-risk areas in South America	NA	5 case-control	NA	<u>Almost daily/daily *vs.* never/rarely</u> Overall – OR=1.42 (1.03-1.94) Men – OR=1.57 (1.09-2.26) Women – OR=1.09 (0.56-2.10)
BARBECUE						
Castellsagué, 2000a[78]	ESCC (risk)	Pooled analysis of hospital-	NA	5 case-control	NA	<u>Almost daily/daily *vs.* never/rarely</u> Overall – OR=1.22 (0.85-1.76)

		based case-control studies conducted in high-risk areas in South America				Men – OR=1.44 (0.95-2.18) Women – OR=0.87 (0.35-2.15)
CEREALS						
Castellsagué, 2000a[78]	ESCC (risk)	Pooled analysis of hospital-based case-control studies conducted in high-risk areas in South America	NA	5 case-control	NA	Almost daily/daily *vs.* never/rarely Overall – OR=0.64 (0.38-1.10) Men – OR=0.61 (0.33-1.12) Women – OR=0.49 (0.14-1.66)
DIETARY FIBER						
Coleman, 2013[84]	ESCC, EAC (risk)	MEDLINE, EMBASE, WEB OF SCIENCE (inception-2012) Citation tracking	*Dietary fibre/fiber,fibre/fiber,cellulose,cereal fibre/fiber, fruit fibre/fiber, vegetable fibre/fiber, soluble fibre/fiber, insoluble fibre/fiber; (o)esophageal neoplasm(s), (o)esophageal cancer, (o)esophageal adenocarcinoma, (o)esophageal squamous cell carcinoma, Barrett('s) (o)esophagus, columnar lined epithelium, specialized intestinal metaplasia, (o)esophageal squamous dysplasia* No language restrictions	13 case-control	No	Highest *vs.* lowest total dietary fiber intake EAC – RR=0.66 (0.44-0.98), n=8, I^2=83% ESCC – RR=0.61 (0.31-1.20), n=5, I^2=87% Egger test: p=0.51
SALT INTAKE						
Castellsagué, 2000a[78]	ESCC (risk)	Pooled analysis of hospital-based case-control studies conducted in high-risk areas in South America	NA	5 case-control	NA	Almost daily/daily *vs.* 1-3/week or month Overall – OR=1.94 (1.40-2.69) Men – OR=2.11 (1.48-3.01) Women – OR=1.17 (0.45-3.04)
ZINC INTAKE						
Li, 2014[87]	EC, ESCC, EAC (risk)	MEDLINE, EMBASE (inception-2013) Citation tracking	*"zinc" OR "zn"; "colorectal" OR "colon" OR "rectal"; "gastric" OR "stomach", "esophagus" OR "esophageal squamous cell carcinoma", "cancer" OR "tumor" OR "carcinoma" OR "neoplasm"* Restricted to studies published in English or Chinese	6 case-control	Newcastle-Ottawa scale	Highest *vs.* lowest zinc intake All studies – RR=0.72 (0.44-1.17), n=6, I^2=74.5%, no publication bias ACCORDING TO TUMOR TYPE EAC – RR=0.96 (0.57-1.62), I^2=73.1% ESCC – RR=0.79 (0.43-1.47), I^2=71.5% ACCORDING TO GEOGRAPHIC AREA Asia – RR=0.43 (0.21-0.86), I^2=44.1% America and Europe – RR=0.89 (0.55-1.45), I^2=72.9%

FOLATE						
Larsson, 2006[94]	EC, ESCC, EAC (risk)	MEDLINE (1966-2006) Citation tracking	*folate, folic acid, or MTHFR in combination with cancer, neoplasm, or the individual cancer sites* No language restrictions	7 case-control	No	Highest *vs.* lowest dietary intake All studies – RR=0.62 (0.53-0.72), n=7, I^2=0%, Egger test: p=0.33 ACCORDING TO TUMOR TYPE EAC – RR=0.50 (0.39-0.65), n=3, I^2=0% ESCC – RR=0.66 (0.53-0.83), n=4, I^2=0% ACCORDING TO STUDY DESIGN Population-based – RR=0.52 (0.42-0.65), n=3 Hospital-based – RR=0.74 (0.59-0.92), n=4
Liu, 2011[101]	EC (risk)	MEDLINE, EMBASE, CBD (inception-2011)	Not specified	6 case-control	No	Highest *vs.* lowest dietary intake OR=0.60 (0.50-0.70), n=8
Tio, 2014[95]	EC, ESCC, EAC (risk)	MEDLINE (1946-2013), EMBASE (1949-2013), CCC (1998-2013) Citation tracking	*folate, folic acid, or vitamin B9, and esophageal, gastric, stomach, or pancreatic cancer, neoplasm, squamous cell carcinoma, or adenocarcinoma*	9 case-control	No	Highest *vs.* lowest dietary intake Overall – OR=0.59 (0.51-0.69), n=9, I^2=21.1%, Egger test: p=0.09 ESCC – OR=0.63 (0.44-0.89), n=4, I^2=47.7%, Egger test: p=0.12 EAC – OR=0.57 (0.43-0.76), n=3, I^2=44.9%, Egger test: p=0.85
ACRYLAMIDE						
Pelucchi, 2011[86]	EC, ESCC, EAC (risk)	MEDLINE (inception-2009), Web site established by World Health Organization and Food and Agricultural Organization for acrylamide research Citation tracking	*(acrylamide OR glycidamide) AND (cancer OR neoplasm OR tumor)* No language restrictions	2 1 cohort 1 case-control	No	Highest *vs.* lowest level of intake RR=0.93 (0.66-1.31), n=2 10 µg/day increase in exposure RR=0.98 (0.91-1.06), n=2 EAC – RR=1.00 (0.85-1.17), n=1 ESCC – RR=0.95 (0.78-1.16), n=1 High *vs.* low intake of fried/baked potatoes RR=1.0 (0.7-1.5), n=1
Pelucchi, 2015[85]	EC (risk)	MEDLINE, EMBASE (2009-2014) Citation tracking	*(acrylamide OR glycidamide) AND (cancer OR neoplasm OR tumor) AND (diet OR dietary OR food OR foods)* No language restrictions	4 2 cohort 2 case-control	No	Highest *vs.* lowest level of intake RR=1.14 (0.93-1.38), n=4 Never/former smokers – RR=1.27 (0.91-1.77), n=3 ACCORDING TO STUDY DESIGN

						Cohort – RR=1.01 (0.71-1.43), n=2 Case-control – RR=1.20 (0.94-1.53), n=2 <u>10 µg/day increase in intake</u> RR=1.03 (0.99-1.07), n=4
ANTIOXIDANTS						
Kubo, 2007[98]	EAC (risk)	MEDLINE (1966-2006), WEB OF SCIENCE Citation tracking	*medical subject headings (MeSH) or keywords "Esophag∗ AND (adenocarcinoma OR carcinoma OR cancer)" combined with any combination of the following terms: antioxidant, ascorbic acid, vitamin C, vitamin E, selenium, carotenoids, beta-carotene, or vitamin A; a similar search was performed using the word "oesophagus," a common British spelling for esophagus; identical searches were performed using "gastric cardia and (adenocarcinoma OR carcinoma OR cancer)"* No language restrictions	5 case-control	No	<u>Highest *vs.* lowest dietary intake</u> Vitamin C – RR=0.49 (0.39-0.62), n=4 Vitamin E – RR=0.80 (0.63-1.03), n=3 Beta-carotene/Vitamin A – RR=0.46 (0.36-0.59), n=4
CAROTENOIDS						
Ge, 2013[88]	EC, ESCC, EAC (risk)	MEDLINE, COCHRANE, WEB OF SCIENCE, SCOPUS, CNKI, CBM (inception-2012) Citation tracking	*"Esophageal Neoplasms", "esophag*" and the British spelling form "oesophag*" with combination of any of the following terms: "cancer", "tumor", "carcinoma", "neoplasm", and "malignancy" OR "cancer of esophagus" AND carotenoids, including alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, zeaxanthin, lycopene* No language restrictions	10 1 cohort 9 case-control	No	<u>Highest *vs.* lowest beta-carotene intake</u> All studies – OR=0.58 (0.44-0.77), n=10, I^2=78.2% ACCORDING TO STUDY DESIGN Cohort – OR=0.85 (0.38-1.90), n=1 Population-based case-control – OR=0.48 (0.39-0.57), n=5, I^2=0.0%, Egger test: p=0.114, Begg test: p=0.142 Hospital-based case-control – OR=0.71 (0.42-1.22), n=5, I^2=88.3%, Egger test: p=0.800, Begg test: p=0.327 ACCORDING TO TUMOR TYPE EAC – OR=0.46 (0.36-0.58), n=4, I^2=0.0%, Egger test: p=0.962, Begg test: p=1.000 ESCC– OR=0.69 (0.45-1.07), n=6, I^2=85.2%, Egger test: p=0.801, Begg test: p=0.851 ACCORDING TO GEOGRAPHIC AREA Europe – OR=0.49 (0.37-0.66), n=7, I^2=43.9%, Egger test: p=0.198, Begg test: p=0.133 Asia– OR=0.91 (0.61-1.36), n=2, I^2=9.5%, Begg test: p=0.317 North America– OR=0.45 (0.36-0.56), n=3, I^2=0.0%, Egger test: p=0.210, Begg test: p=0.117

						South America– OR=1.47 (1.07-2.02), n=1 <u>Highest *vs.* lowest alpha-carotene intake</u> All studies – OR=0.81 (0.70-0.94), n=3, I^2=0.0% ESCC – OR=0.82 (0.70-0.95), I^2=0.0% <u>Highest *vs.* lowest lycopene intake</u> All studies – OR=0.75 (0.64-0.86), n=2, I^2=0.0% ESCC – OR=0.74 (0.64-0.86), I^2=0.0% <u>Highest *vs.* lowest beta-cryptoxanthin intake</u> All studies – OR=0.80 (0.66-0.97), n=3, I^2=50.9% ESCC – OR=0.83 (0.72-0.97), I^2=42.6% <u>Highest *vs.* lowest lutein and zeaxanthin intake</u> All studies – OR=0.71 (0.59-0.87), n=2, I^2=0.0%
MATÉ						
Castellsagué, 2000a[78]	ESCC (risk)	Pooled analysis of hospital-based case-control studies conducted in high-risk areas in South America	NA	5 case-control	NA	<u>Ever *vs.* never maté drinker</u> Overall – OR=1.52 (1.10-2.12) Men – OR=1.34 (0.92-1.96) Women – OR=2.20 (1.08-4.47) <u>Ex- *vs.* never maté drinker</u> Overall – OR=1.87 (1.25-2.80) Men – OR=1.91 (1.20-3.06) Women – OR=1.74 (0.73-4.11) <u>Current *vs.* never maté drinker</u> Overall – OR=1.47 (1.06-2.05) Men – OR=1.27 (0.87-1.87) Women – OR=2.30 (1.13-4.71) <u>Maté amount (l/day)</u> *Overall* 0.01-0.50 – OR=1.39 (0.98-1.98) 0.51-1.00 – OR=1.34 (0.95-1.90) 1.01-1.50 – OR=1.96 (1.27-3.03) 1.51-2.00 – OR=2.03 (1.32-3.13) > 2.00 – OR=3.04 (1.84-5.02) *Men*

	0.01-0.50 – OR=1.23 (0.81-1.86) 0.51-1.00 – OR=1.20 (0.80-1.79) 1.01-1.50 – OR=1.69 (1.03-2.77) 1.51-2.00 – OR=1.69 (1.03-2.77) > 2.00 – OR=2.30 (1.32-4.03) *Women* 0.01-0.50 – OR=1.93 (0.92-4.08) 0.51-1.00 – OR=1.86 (0.85-4.05) 1.01-1.50 – OR=4.03 (1.47-11.04) 1.51-2.00 – OR=3.95 (1.53-10.20) > 2.00 – OR=11.65 (2.96-45.79) <u>Years of maté drinking</u> *Overall* 1-29 – OR=1.40 (0.91-2.13) 30-39 – OR=1.39 (0.93-2.07) 40-49 – OR=1.53 (1.06-2.21) 50-59 – OR=1.47 (1.00-2.17) > 60 – OR=1.92 (1.25-2.96) *Men* 1-29 – OR=1.23 (0.76-2.00) 30-39 – OR=1.32 (0.85-2.07) 40-49 – OR=1.38 (0.91-2.10) 50-59 – OR=1.27 (0.81-1.98) > 60 – OR=1.61 (0.96-2.72) *Women* 1-29 – OR=1.83 (0.69-4.88) 30-39 – OR=1.28 (0.49-3.37) 40-49 – OR=2.10 (0.91-4.87) 50-59 – OR=2.39 (1.06-5.37) > 60 – OR=2.71 (1.18-6.22) <u>Years since quitting</u> *Overall* 1-9 – OR=1.53 (1.07-2.19) ≥ 10 – OR=0.90 (0.59-1.36) *Men* 1-9 – OR=1.78 (1.16-2.74) ≥ 10 – OR=1.07 (0.67-1.69)

						Women 1-9 – OR=1.11 (0.55-2.25) ≥ 10 – OR=0.39 (0.14-1.09) <u>Maté temperature</u> *Overall* Hot – OR=1.11 (0.84-1.47) Very hot – OR=1.89 (1.24-2.86) *Men* Hot – OR=1.06 (0.77-1.45) Very hot – OR=1.77 (1.09-2.86) *Women* Hot – OR=1.33 (0.71-2.49) Very hot – OR=2.47 (1.03-5.91) <u>Joint effects of maté amount and temperature (reference category: ≤0.50 l/day & Cold/warm/hot)</u> ≤0.50 & Very hot – OR=0.99 (0.48-2.02) 0.51-1.00 & Cold/warm/hot – OR=0.91 (0.71-1.16) 0.51-1.00 & Very hot – OR=1.59 (0.96-2.63) 1.01-1.50 & Cold/warm/hot – OR=1.50 (1.05-2.14) 1.01-1.50 & Very hot – OR=0.73 (0.24-2.26) >1.50 & Cold/warm/hot – OR=1.38 (1.00-1.90) >1.50 & Very hot – OR=4.14 (2.24-7.67) <u>Ever *vs.* never any very hot beverage (other than maté)</u> Overall – OR=2.45 (1.72-3.49) Men – OR=2.28 (1.48-3.50) Women – OR=3.21 (1.66-6.23) <u>Ever *vs.* never any very hot beverage (including maté)</u> Overall – OR=2.07 (1.55-2.76) Men – OR=2.10 (1.49-2.96) Women – OR=2.18 (1.20-3.94)
WCRF, 2007[22]	EC (risk, incidence, mortality)	MEDLINE, WEB OF SCIENCE, CINAHL,	*Not specifically stated* No language restrictions	5 case-control	No	<u>Per 1 cup/d increment</u> RR=1.16 (1.07-1.25), n=5, I^2=88.7%

		BIOSIS, CAB Abstracts, LILACS, EMBASE COCHRANE (inception-2006) Citation tracking				
Andrici, 2013[97]	ESCC (risk)	MEDLINE (1946-2012), EMBASE (1949-2012), CCC (1998-2012) Citation tracking	*'Ilex paraguariensis' OR 'maté' OR 'yerba maté' OR 'erva maté' OR 'chimarraõ' OR 'cimarrón' AND 'cancer' OR 'neoplasms'* No language restrictions	9 case-control	No	<u>Ever *vs.* never maté intake</u> All studies – OR=2.57 (1.66-3.98), n=9, I^2=65.4%, Egger test: p=0.229 Adjusted results – OR=2.95 (1.70-5.13), n=5, I^2=49.4% Unadjusted results – OR=2.31 (1.18-4.54), n=5, I^2=74.0% <u>Highest *vs.* lowest maté intake</u> All studies – OR=2.76 (1.33-5.73), n=6, I^2=74.3%
TEA						
Castellsagué, 2000a[78]	ESCC (risk)	Pooled analysis of hospital-based case-control studies conducted in high-risk areas in South America	NA	5 case-control	NA	<u>Ever *vs.* never tea drinker</u> Overall – OR=0.81 (0.62-1.06) Men – OR=0.80 (0.58-1.10) Women – OR=0.74 (0.45-1.22) <u>Highest amount *vs.* never tea drinker</u> Overall – OR=0.62 (0.40-0.96) Men – OR=0.53 (0.32-0.88) Women – OR=0.96 (0.39-2.34) <u>Highest *vs.* lowest tea temperature</u> Overall – OR=3.73 (1.41-9.89) Men – OR=8.73 (1.95-39.10) Women – OR=2.20 (0.42-11.56)
Ishikawa, 2006[17]	EC (incidence)	Pooled analysis of two prospective cohort studies conducted in Miyagi Prefecture, Japan	*NA*	2 cohort	NA	<u>1-2 cups/day *vs.* never or occasionally green tea consumption</u> HR=1.03 (0.46-2.28) <u>3-4 cups/day *vs.* never or occasionally green tea consumption</u> HR=1.13 (0.53-2.42)

						≥ 5 cups/d *vs.* never or occasionally green tea consumption HR=1.67 (0.89-3.16)
WCRF, 2007[22]	EC (risk, incidence, mortality)	MEDLINE, WEB OF SCIENCE, CINAHL, BIOSIS, CAB Abstracts, LILACS, EMBASE COCHRANE (inception-2006) Citation tracking	*Not specifically stated* No language restrictions	7 case-control	No	Per 1 cup/d increment RR=0.95 (0.88-1.02), n=7, I^2=60.6%
Zheng, 2012[104]	EC (risk)	MEDLINE (1966-2012), EMBASE (1980-2012), SCI (1945-2012), CBD (1981-2012), WANFANG (1980-2012) Citation tracking	*"tea", "food", "diet", "beverage", "drinking" or "tea polyphenol" combined with "esophageal", "oesophageal", or "esophagus"* Restricted to studies published in English or Chinese	10 2 cohort 8 case-control	No	Highest *vs.* lowest green tea intake RR=0.76 (0.49-1.02), n=10, I^2=73%, Egger test: p=0.16, Begg test: p=0.37 ACCORDING TO SEX Men – RR=1.04 (0.48-1.60), n=2, I^2=73% Women – RR=0.32 (0.10-0.54), n=2, I^2=0% ACCORDING TO STUDY DESIGN Cohort – RR=1.67 (0.46-2.87), n=2, I^2=0% Case-control – RR=0.72 (0.45-0.98), n=8, I^2=76% Population-based case-control – RR=0.71 (0.43-0.98), n=7, I^2=78% Hospital-based case-control – RR=0.92 (0.49-2.32), n=1 ACCORDING TO GEOGRAPHIC AREA Japan – RR=1.67 (0.46-2.87), n=2, I^2=0% China – RR=0.73 (0.44-1.02), n=7, I^2=79% Northern Iran – RR=0.65 (0.32-1.31), n=1
Sang, 2013[103]	EC (risk)	MEDLINE, EMBASE, COCHRANE (inception-2012)	*(tea OR catechin OR green tea OR beverages OR diet OR drinking OR lifestyle OR dietary) AND (esophageal OR digestive) AND (cancer OR tumor OR neoplasm OR carcinoma)* Restricted to studies published in English	12 2 cohort 10 case-control	No	Highest *vs.* lowest green tea intake All studies – RR=1.09 (0.76-1.55), n=12, I^2=75.6%, Egger test: p=0.94, Begg test: p=0.945 ACCORDING TO SEX Men – RR=1.06 (0.75-1.52), n=7, I^2=74% Women – RR=0.46 (0.28-0.74), n=2, I^2=0% Both – RR=1.34 (0.88-2.03), n=5, I^2=51.4%

						ACCORDING TO STUDY DESIGN Cohort – RR=1.68 (0.89-3.16), n=2, I^2=0% Case-control – RR=1.01 (0.68-1.50), n=10, I^2=79.1% Population-based case-control – RR=0.80 (0.41-1.56), n=4, I^2=81.1% Hospital-based case-control – RR=1.24 (0.65-2.37), n=5, I^2=83.2% Nested-based case-control – RR=0.87 (0.38-2.01), n=1 ACCORDING TO GEOGRAPHIC AREA China – RR=1.01 (0.63-1.62), n=8, I^2=83.6% Japan – RR=1.42 (0.88-2.28), n=3, I^2=0% Iran – RR=0.89 (0.38-2.09), n=1
Zheng, 2013[89]	EC, ESCC (risk)	MEDLINE, WEB OF SCIENCE, CNKI, VIP (inception-2011) Citation tracking	*(tea OR polyphenol OR catechin, OR coffee OR caffeine OR beverages OR diet OR drinking) AND (esophageal OR esophagus OR oesophagus OR oesophageal) AND (cancer OR neoplasm OR tumor OR carcinoma)* Restricted to studies published in English or Chinese	24 4 cohort 20 case-control	No	<u>Highest *vs.* lowest green tea intake</u> All studies – OR=0.77 (0.57-1.04), n=16, I^2=72.0%, Egger test: p=0.05 Adjusted for tea temperature – OR=0.69 (0.49-0.96), n=3, I^2=69.9% Adjusted for alcohol drinking or smoking – OR=0.81 (0.59-1.09), n=13, I^2=68.8% ACCORDING TO SEX Men – OR=1.07 (0.75-1.52), n=5, I^2=54.0% Women – OR=0.32 (0.17-0.59), n=2, I^2=0.0% Both – OR=0.70 (0.45-1.10), n=9, I^2=75.4% ACCORDING TO STUDY DESIGN Cohort – OR=1.68 (0.89-3.16), n=2, I^2=0.0% Case-control – OR=0.70 (0.51-0.96), n=14, I^2=73.8% Population-based case-control – OR=0.64 (0.43-0.95), n=11, I^2=79.3% Hospital-based case-control – OR=0.86 (0.58-1.25), n=3, I^2=0.0% Case control from China – OR=0.64 (0.44-0.95), n=11, I^2=79.4% Case-control out of China – OR=0.85 (0.57-1.25), n=3, I^2=0.0% ACCORDING TO GEOGRAPHIC AREA China – OR=0.64 (0.44-0.95), n=11, I^2=79.4% Japan – OR=1.10 (0.71-1.72), n=4, I^2=29.7%

						Iran – OR=0.89 (0.38-2.09), n=1 ACCORDING TO TUMOR TYPE ESCC – OR=0.66 (0.33-1.33), n=5, I^2=71.5% Not reported – OR=0.79 (0.56-1.12), n=11, I^2=74.0% <u>Per 2 cups/d increase in green tea intake</u> OR=0.97 (0.87-1.08) <u>Highest *vs.* lowest black tea intake</u> All studies – OR=1.35 (0.86-2.11), n=3, I^2=0.0%, Egger test: p=0.925
COFFEE						
Castellsagué, 2000a[78]	ESCC (risk)	Pooled analysis of hospital-based case-control studies conducted in high-risk areas in South America	NA	5 case-control	NA	<u>Ever *vs.* never coffee drinker</u> Overall – OR=1.04 (0.83-1.30) Men – OR=1.09 (0.84-1.41) Women – OR=0.89 (0.53-1.49) <u>Highest amount *vs.* never coffee drinker</u> Overall – OR=1.26 (0.88-1.81) Men – OR=1.19 (0.80-1.78) Women – OR=1.68 (0.72-3.93) <u>Highest *vs.* lowest coffee temperature</u> Overall – OR=1.01 (0.52-1.98) Men – OR=0.76 (0.35-1.64) Women – OR=3.46 (0.45-26.57) <u>Ever *vs.* never coffee with milk drinker</u> Overall – OR=1.15 (0.94-1.42) Men – OR=1.09 (0.86-1.38) Women – OR=1.44 (0.90-2.29) <u>Highest amount *vs.* never coffee with milk drinker</u> Overall – OR=1.31 (0.89-1.95) Men – OR=1.14 (0.72-1.81) Women – OR=2.12 (0.91-4.93) <u>Highest *vs.* lowest coffee with milk temperature</u> Overall – OR=2.29 (1.37-3.81)

						Men – OR=2.22 (1.20-4.10) Women – OR=2.82 (0.94-8.45)
Turati, 2011[90]	ESCC, EAC (risk)	MEDLINE (inception-2009) Citation tracking	*(coffee OR caffeine OR beverages OR diet OR drinking) AND (oral OR pharyngeal OR oropharyngeal OR oropharynx OR pharynx OR mouth OR hypopharyngeal OR hypopharynx OR laryngeal OR larynx OR head OR neck OR esophagus OR oesophagus OR esophageal OR oesophageal OR aerodigestive) AND (cancer OR carcinoma OR tumor OR neoplasm) AND risk* Restricted to studies published in English	9 1 cohort 8 case-control	No	Highest *vs.* lowest coffee intake EAC – RR=1.18 (0.81-1.71), n=3, I^2=43.7% ESCC – RR=0.87 (0.65-1.17), n=7, I^2=74.6% ESCC (case-control studies) – RR=0.92 (0.67-1.27), n=6 ESCC (cohort studies) – RR=0.60 (0.37-0.97), n=1
Yu, 2011[102]	EC (incidence)	MEDLINE (1966-2010), EMBASE (1985-2010), SCIE (1945-2010) Citation tracking	*coffee combined with cancer or neoplasm or carcinoma* Restricted to studies published in English	2 cohort	No	Highest *vs.* lowest coffee intake RR=0.55 (0.37-0.74), n=2, I^2=0.0%
Zheng, 2013[89]	EC, ESCC, EAC (risk)	MEDLINE, WEB OF SCIENCE, CNKI, VIP (inception-2011) Citation tracking	*(tea OR polyphenol OR catechin, OR coffee OR caffeine OR beverages OR diet OR drinking) AND (esophageal OR esophagus OR oesophagus OR oesophageal) AND (cancer OR neoplasm OR tumor OR carcinoma)* Restricted to studies published in English or Chinese	24 4 cohort 20 case-control	No	Highest *vs.* lowest coffee intake All studies – OR=0.88 (0.76-1.01), n=17, I^2=38.4%, Egger test: p=0.53 Adjusted for alcohol drinking or smoking – OR=0.89 (0.77-1.03), n=16, I^2=37.6% ACCORDING TO SEX Men – OR=0.82 (0.58-1.15), n=4, I^2=48.6% Women – OR=1.68 (0.72-3.93), n=1 Both – OR=0.88 (0.75-1.04), n=12, I^2=36.6% ACCORDING TO STUDY DESIGN Cohort – OR=0.88 (0.65-1.19), n=5, I^2=31.3% Case-control – OR=0.88 (0.74-1.04), n=12, I^2=44.8% ACCORDING TO GEOGRAPHIC AREA Asia – OR=0.67 (0.55-0.82), n=7, I^2=0.0% Europe – OR=0.95 (0.78-1.15), n=6, I^2=38.5% Others – OR=1.13 (0.82-1.57), n=4, I^2=40.3% ACCORDING TO TUMOR TYPE EAC – OR=0.88 (0.67-1.17), n=3, I^2=55.5% ESCC – OR=1.00 (0.80-1.25), n=8, I^2=44.1% Not reported – OR=0.69 (0.56-0.87), n=6, I^2=0.0%

						Per 2 cups/d increase in coffee intake OR=1.00 (0.89-1.12)
SOFT DRINKS						
Boyle, 2014[91]	EC, ESCC, EAC (risk)	MEDLINE, ISI WEB OF KNOWLEDGE (inception-2012) Citation tracking	*With the key words 'carbonated beverages', 'carbonated soda', 'carbonated sodas', 'coca cola', 'coca-cola', 'soft drinks', 'carbonated drinks', 'carbonated soft drinks', 'soft drink consumption', 'cola beverages', 'sweetened beverages', 'sugar-sweetened', 'sports drinks', 'soda pop', 'fizzy drinks', 'tonic', 'cancer', 'neoplasms'* No language restrictions.	5 1 cohort 4 case-control	No	Highest *vs.* lowest intake *EC* RR=0.82 (0.57-1.20), n=4, I^2=0% *EAC* RR=0.80 (0.45-1.41), n=4, I^2=55% *ESCC* RR=0.73 (0.46-1.15), n=4, I^2=18%
HOT BEVERAGES AND FOODS						
Chen, 2015[105]	EC, ESCC, EAC (risk)	MEDLINE (inception-2014), EMBASE (inception-2014), ISI WEB OF KNOWLEDGE (inception-2014) Citation tracking	*using the string '(esophageal OR oesophageal) AND (cancer OR carcinoma OR neoplasm) AND (tea OR maté OR coffee OR beverage OR liquid OR alcohol OR food OR diet)'* Restricted to studies published in English	39 case-control	Newcastle-Ottawa scale	Hot beverages and/or foods *EC* All studies – OR=1.82 (1.53-2.17), n=39, I^2=90.3%, Egger test: p=0.121, Begg test: p=0.557 ACCORDING TO SEX Men – OR=2.36 (1.53-3.65), n=8, I^2=87.6% Women – OR=2.45 (1.51-3.98), n=7, I^2=85.6% Both – OR=1.78 (1.49-2.16), n=37, I^2=89.3% ACCORDING TO STUDY QUALITY Score ≥ 7 – OR=2.73 (2.06-3.62), n=2, I^2=12.9% Score < 7 – OR=1.78 (1.49-2.14), n=45, I^2=90.4 ACCORDING TO GEOGRAPHIC AREA Asia – OR=2.06 (1.62-2.61), n=28, I^2=91.7% South America – OR=1.52 (1.25-1.85), n=13, I^2=66.7% Europe – OR=0.95 (0.68-1.34), n=5, I^2=62.4% Africa – OR=12.78 (6.95-23.50), n=1 ACCORDING TO TUMOR TYPE ESCC – OR=1.60 (1.29-2.00), n=26, I^2=88.7% EAC – OR=0.79 (0.53-1.16), n=4, I^2=50.3% Not reported – OR=2.35 (1.90-2.91), n=20, I^2=80.7% Hot beverages All studies – OR=1.77 (1.39-2.25), n=23, I^2=92.8%

	Tea – OR=1.88 (1.16-3.07), n=8, I^2=94.3% Maté – OR=1.72 (1.43-2.07), n=10, I^2=47.5% <u>Hot foods</u> All studies – OR=2.09 (1.71-2.56), n=10, I^2=57.8% <u>Hot beverages and foods</u> All studies – OR=1.73 (1.18-2.53), n=7, I^2=68.2%

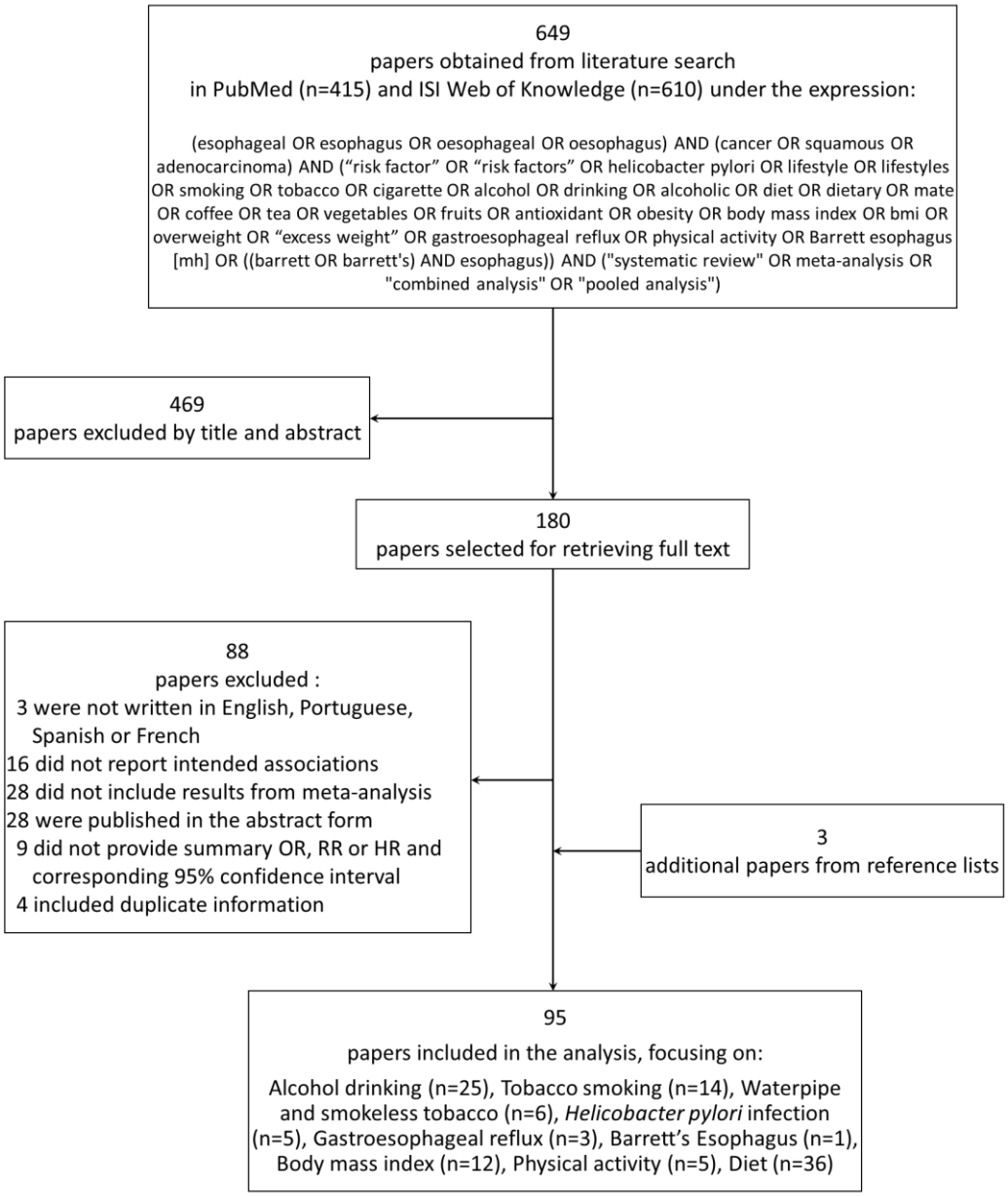
EC: esophageal cancer; EAC: esophageal adenocarcinoma; ESCC: esophageal squamous cell carcinoma; NA: Not available; CI: confidence interval; n: number of studies; I^2: heterogeneity statistic (percentage of variance in a meta-analysis that is attributable to study heterogeneity); RR: relative risk; OR: odds ratio; HR: hazard ratio; IR: incidence rate; S: synergy index (ratio of the observed excess risk in individuals exposed to both factors relative to the expected excess risk assuming that both exposures are independent risk factors).

Supplementary Table 2: Quality assessment of the studies included in the systematic review, using the AMSTAR tool. For each question, answer "yes" was marked with a plus, "no" with a cross, and "not applicable" with a triangle.

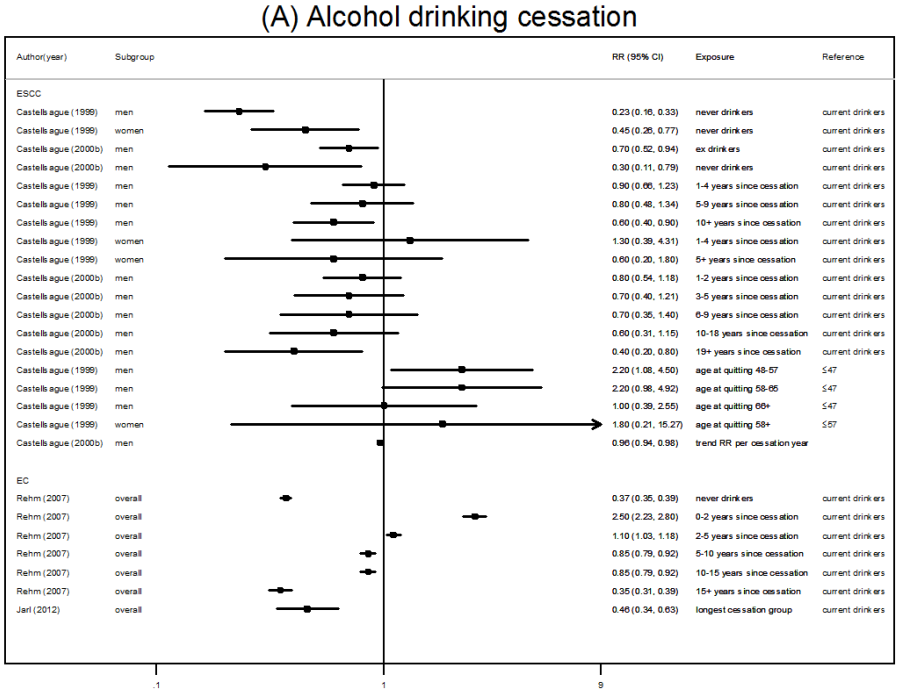
	1. Was an 'a priori' design provided?	2. Was there duplicate study selection and data extraction?	3. Was a comprehensive literature search performed?	4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5. Was a list of studies (included and excluded) provided?	6. Were the characteristics of the included studies provided?	7. Was the scientific quality of the included studies assessed and documented?	8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	9. Were the methods used to combine the findings of studies appropriate?	10. Was the likelihood of publication bias assessed?	11. Was the conflict of interest included?	Final score
Holman, 1996[16]	+	×	×	×	×	×	×	×	+	×	+	3/11
Castellsague, 1999[26]	+	⚠	⚠	⚠	⚠	+	×	×	×	×	+	3/7
Corrao, 1999[14]	+	+	×	×	×	+	+	+	+	+	+	8/11
Bosetti, 2000[13]	+	⚠	⚠	⚠	⚠	×	×	×	×	×	+	2/7
Castellsague, 2000a[78]	+	⚠	⚠	⚠	⚠	+	×	×	×	×	+	3/7
Castellsague, 2000b[27]	+	⚠	⚠	⚠	⚠	×	×	×	×	×	+	2/7
Bagnardi, 2001[12]	+	+	×	×	×	+	×	×	+	×	+	5/11
Riboli, 2003[76]	+	×	×	×	+	×	×	×	+	+	+	5/11
Zeka, 2003[23]	+	×	×	×	×	+	×	×	+	×	+	4/11
Corrao, 2004[15]	+	+	+	×	×	+	+	+	+	×	+	8/11
Hampel, 2005[61]	+	+	×	×	×	+	×	×	+	+	+	6/11
Lock, 2005[75]	+	×	+	×	×	+	×	×	+	×	+	5/11
Ishikawa, 2006[17]	+	⚠	⚠	⚠	⚠	+	×	×	×	×	×	2/7
Kubo, 2006[63]	+	+	+	+	+	+	×	×	+	+	+	9/11
Larsson, 2006[94]	+	×	×	×	+	+	×	×	+	+	+	6/11
Kubo, 2007[98]	+	+	+	+	+	+	×	×	+	+	+	9/11
Rehm, 2007[43]	+	×	+	×	×	+	×	×	×	×	+	4/11
Rokkas, 2007[51]	+	+	+	×	×	+	×	×	+	+	×	6/11
Thomas, 2007[57]	+	+	+	×	×	+	×	×	+	+	+	7/11
WCRF, 2007[22]	+	×	×	+	×	+	×	×	+	+	×	5/11
Boffetta, 2008[47]	×	×	+	×	×	+	×	×	+	×	+	4/11
Gandini, 2008[39]	+	×	×	×	×	×	×	×	+	+	+	4/11
Islami, 2008[50]	+	+	+	×	+	+	×	×	+	+	+	8/11
Renehan, 2008[59]	+	+	+	×	+	+	+	+	+	+	+	10/11
Smith, 2008[60]	+	×	×	×	+	+	×	×	+	×	+	5/11
Zhuo, 2008[53]	+	+	+	×	×	×	×	×	+	+	+	6/11
Ansary-Moghaddam, 2009a[36]	+	×	+	×	×	+	×	×	+	+	+	6/11
Ansary-Moghaddam, 2009b[37]	+	⚠	⚠	⚠	⚠	+	×	×	×	×	+	3/7
Guh, 2009[58]	+	+	+	×	×	+	×	×	+	+	+	7/11
Islami, 2009[81]	+	+	+	×	+	+	×	×	+	+	+	8/11

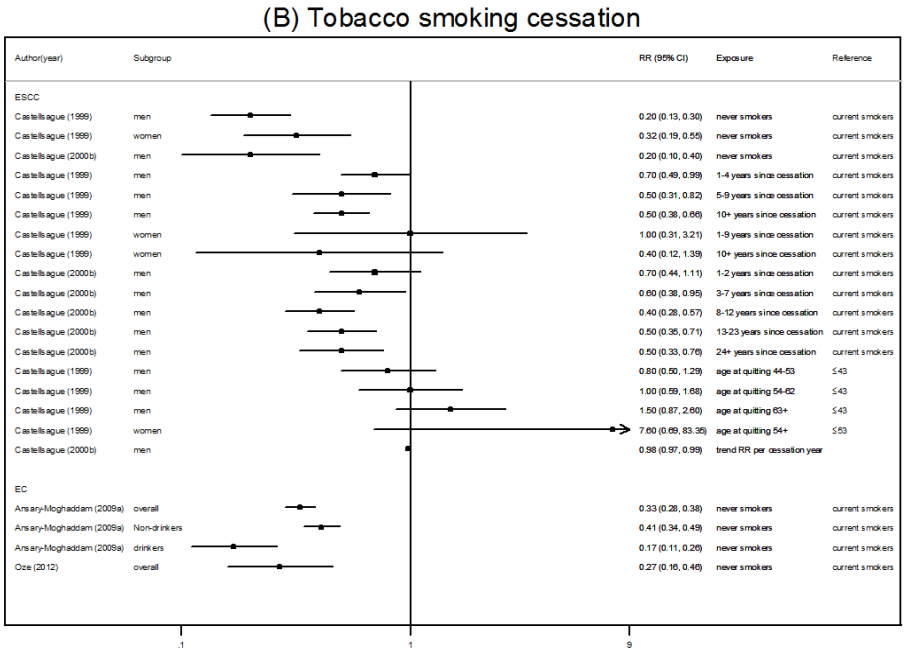

Lee, 2009[48] 5/11
Mulholland, 2009[71] 8/11
Akl, 2010[44] 9/11
Cook, 2010[38] 4/7
Rota, 2010[33] 3/11
Rubenstein, 2010[55] 7/11
Soerjomataram, 2010[77] 3/11
Freedman, 2011[29] 4/7
Islami, 2011[30] 6/11
Lee, 2011[46] 4/11
Li, 2011[19] 6/11
Liu, 2011[101] 6/11
Oze, 2011[20] 6/11
Pelucchi, 2011[86] 8/11
Tramacere, 2011[41] 5/11
Turati, 2011[90] 5/11
Yu, 2011[102] 7/11
Hoyo, 2012[62] 4/7
Jarl, 2012[42] 5/11
Lubin, 2012[31] 3/7
Oze, 2012[40] 6/11
Tramacere, 2012[35] 6/11
Yu, 2012[73] 6/11
Zheng, 2012[104] 7/11
Akhtar, 2013[45] 6/11
Andrici, 2013[97] 7/11
Bagnardi, 2013[24] 6/11
Choi, 2013[92] 9/11
Coleman, 2013[84] 7/11
Dobbins, 2013[66] 6/11
Ge, 2013[88] 8/11
Han, 2013[96] 7/11
Huang, 2013[99] 7/11
Liu, 2013[79] 7/11
Prabhu, 2013[32] 8/11
Qu, 2013[93] 7/11
Salehi, 2013[82] 9/11
Sang, 2013[103] 8/11
Singh, 2013[65] 9/11
Turati, 2013[64] 6/11
Xie, 2013[52] 6/11
Zheng, 2013[89] 7/11
Behrens, 2014[67] 9/11
Boyle, 2014[91] 7/11
Chen, 2014[68] 10/11
Cook, 2014[56] 4/7

Li, 2014[80]		9/11
Li, 2014[87]		9/11
Li, 2014[18]		9/11
Liu, 2014[74]		9/11
Nie, 2014[54]		8/11
Prabhu, 2014[4]		9/11
Schmid, 2014[69]		9/11
Singh, 2014[70]		10/11
Tio, 2014[95]		7/11
Yu, 2014[100]		7/11
Zhu, 2014[83]		9/11
Bagnardi, 2015[25]		5/11
Chen, 2015[105]		8/11
Drahos, 2015[34]		3/7
Fahey, 2015[28]		8/11
Pelucchi, 2015[85]		5/11
Roerecke, 2015[21]		8/11
Siddiqi, 2015[49]		8/11
Turati, 2015[72]		7/11

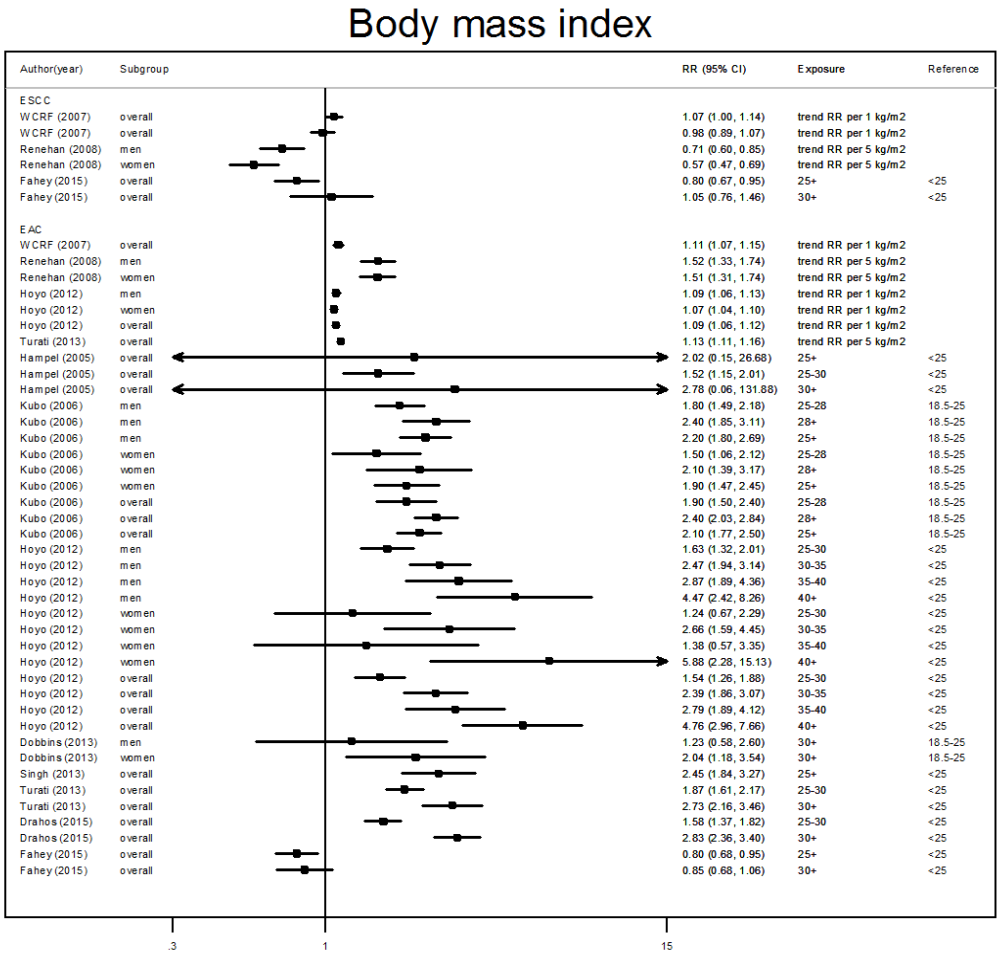


Supplementary Figure 1: Flow-chart of the systematic review.

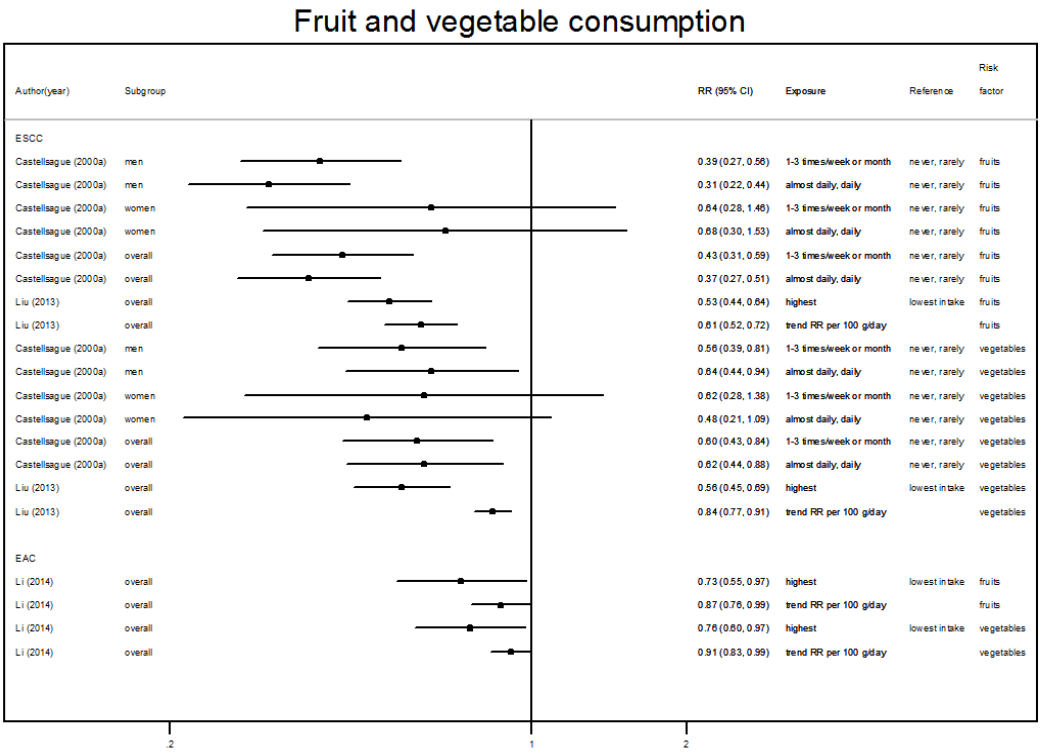




Supplementary Figure 2: Forests plots of overall and sex-specific associations between alcohol drinking cessation (A) and tobacco smoking cessation (B) and the occurrence of esophageal cancer. RR: relative risk, CI: confidence interval, ESCC: esophageal squamous cell carcinoma, EC: esophageal cancer.



Supplementary Figure 3: Forest plot of overall and sex-specific associations between BMI and the occurrence of esophageal cancer, by histological subtype. RR: relative risk, CI: confidence interval, ESCC: esophageal squamous cell carcinoma, EAC: esophageal adenocarcinoma.



Supplementary Figure 4: Forest plot of overall and sex-specific associations between fruit and vegetable consumption and the occurrence of esophageal cancer, by histological subtype. RR: relative risk, CI: confidence interval, ESCC: esophageal squamous cell carcinoma, EAC: esophageal adenocarcinoma.

Paper V

Castro C, Peleteiro B, Morais S, Severo M, Bento MJ, Lunet N.

AN EXPLANATORY AND PREDICTIVE MODEL OF THE VARIATION IN ESOPHAGEAL CANCER INCIDENCE, BASED ON CHANGES IN THE EXPOSURE TO RISK FACTORS.

(submitted)

AN EXPLANATORY AND PREDICTIVE MODEL OF THE VARIATION IN ESOPHAGEAL CANCER INCIDENCE, BASED ON CHANGES IN THE EXPOSURE TO RISK FACTORS

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ABSTRACT

Background: Variations in the exposure to risk factors may be used to explain past cancer trends and to predict its future burden. This study aimed to develop a model able to describe and predict the variation of esophageal cancer incidence in 1995-2005, taking into account changes in exposures to risk factors in different countries.

Methods: We adapted an existing model to calculate the expected variation in the number of esophageal cancer cases, between 1995 and 2005, in Australia, Japan, Italy, Portugal, the United Kingdom (UK) and the United States of America, due to changes in exposures to risk factors, taking into account the corresponding lag times. Analyses were based on country-specific data of cancer incidence and exposures to risk factors. We computed 95% credibility intervals for each estimate through Monte Carlo simulation methods.

Results: Absolute deviations between the number of cases predicted and those observed in 2005 ranged between 1.8% in Japan and 23.6% in the UK among men; 0.0% in Japan and 18.0% in Australia among women. In Italy and Japan, deviations did not exceed 3%. The UK registered the worst model performance. The variation in esophageal cancer incidence was mainly influenced by changes in fruit and red meat intake, and body mass index. For nearly half of the sex- and histological type-specific predictions performed, the credibility intervals included the observed number of cases.

Conclusion: This study proposes a framework for the analysis of the contribution of changes in exposure to different factors to esophageal cancer incidence trends and for long-term predictions at a population level.

KEYWORDS

Esophageal Neoplasms; Adenocarcinoma; Carcinoma, Squamous Cell; Population Attributable Fractions.

INTRODUCTION

Esophageal cancer is one of the most lethal cancers[1], with relatively small differences in survival across the most developed countries and over time[2, 3]. Squamous cell carcinoma (ESCC) and adenocarcinoma (EAC) are the major histological types of esophageal cancer. These show markedly different incidence and mortality trends, reflecting essentially differences in the contribution of the different risk factors to their occurrence in distinct settings[4]. While smoking and a low consumption of fruits and vegetables increase the risk of both subtypes, alcohol drinking increases ESCC risk, but not EAC, which is associated with overweight/obesity and gastroesophageal reflux (GERD)[5-8].

Some studies have evaluated the impact of the exposure to risk factors on esophageal cancer incidence/mortality rates at a given time through the corresponding population attributable fractions (PAFs)[9, 10]. However, to our knowledge, the relation between the trends in the exposures to all major determinants of esophageal cancer and the variation in its incidence has not been comprehensively assessed. Furthermore, the most widely used models to predict future cancer rates incorporate age, period and/or cohort effects[11-14], instead of the actual variations in the exposure to risk factors.

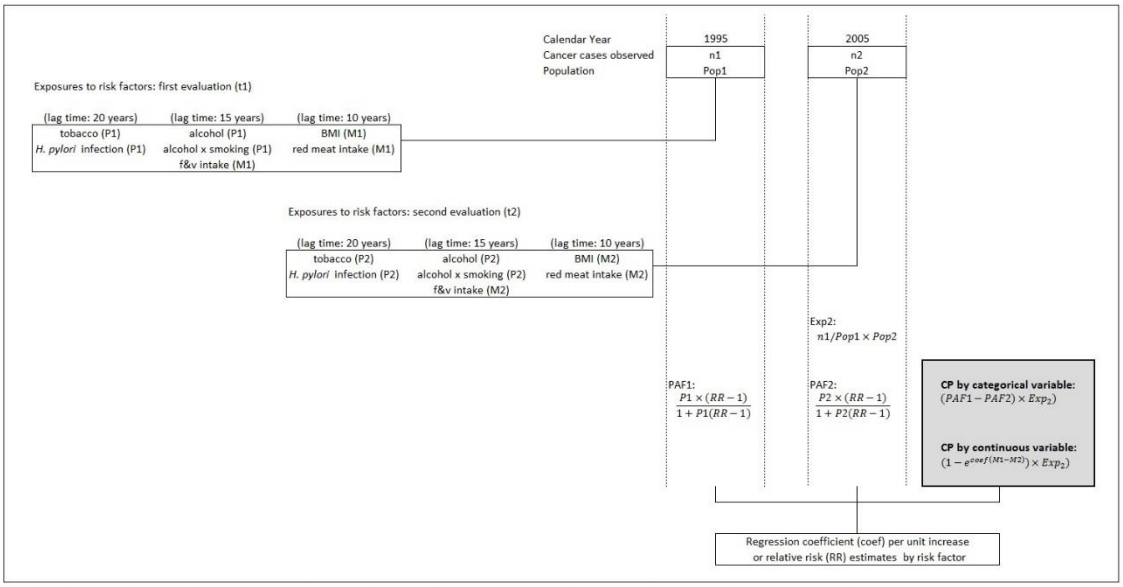
This study aimed to develop a model able to describe and predict the variation of esophageal cancer incidence by histological type in different countries, namely Australia, Italy, Japan, Portugal, the United Kingdom (UK) and the United States of America (USA), taking into account the changes in the exposures to risk factors in each setting.

METHODS

We adapted an existing model (IMPACT), which was originally developed to explain the trends in mortality from a non-communicable disease other than cancer, namely coronary heart disease; after its validation, this model has been used in several countries[15, 16]. Briefly, it calculates the number of deaths prevented or postponed which are explained by changes in past exposures to different risk factors and treatments, and then provides a combined overall estimate.

Using a similar methodological approach, we developed a model to explain and predict esophageal cancer incidence. We calculated the number of esophageal cancer cases prevented

(CP) between 1995 and 2005, in individuals aged 15 years or older, based on past exposures to risk factors, as summarized in Figure 1; positive figures for CP indicate that the number of cases decreased due to the variation in exposure to the risk factors, whereas negative values reflect an increase in incidence. The risk factors considered in the present study were the following: tobacco smoking, body mass index (BMI), and fruit, vegetable and red meat consumption for both histological subtypes; *Helicobacter pylori* (*H. pylori*) infection for EAC alone; and alcohol drinking and its interaction with smoking for ESCC alone.



H. pylori : *Helicobacter pylori* ; BMI: body mass index; f&v: fruit and vegetable intake; M1/M2: mean exposure to risk factor in time t1/t2; P1/P2: prevalence of exposure to risk factor in time t1/t2; Exp2: Cancer cases expected in t2; PAF: population attributable fraction; CP: cases prevented.

Figure 1: Data required for the proposed model and methods for the calculation of the number of cases prevented (CP) due to variations in exposure to risk factors.

Association between modifiable exposures and esophageal cancer

Estimates of the magnitude of association between these factors and ESCC and/or EAC were obtained from published meta-analyses, by sex, whenever available, or overall, otherwise. Regarding fruit and vegetable intake, estimates were obtained by geographical area (Asia, Europe and the USA), for esophageal cancer as a whole[17]; no specific estimate was found for Australia, so the overall relative risks (RR) estimates were used[17]. Cohort studies included in the selected meta-analyses were assessed to estimate the most likely lags between exposure and outcome, based on the magnitude of the effects found in studies with different follow-up periods. The RR estimates, the lag periods considered for each combination of risk factor and the respective outcome, as well as the corresponding sources of information are summarized in Supplemental Table 1.

Prevalence of exposure to risk factors

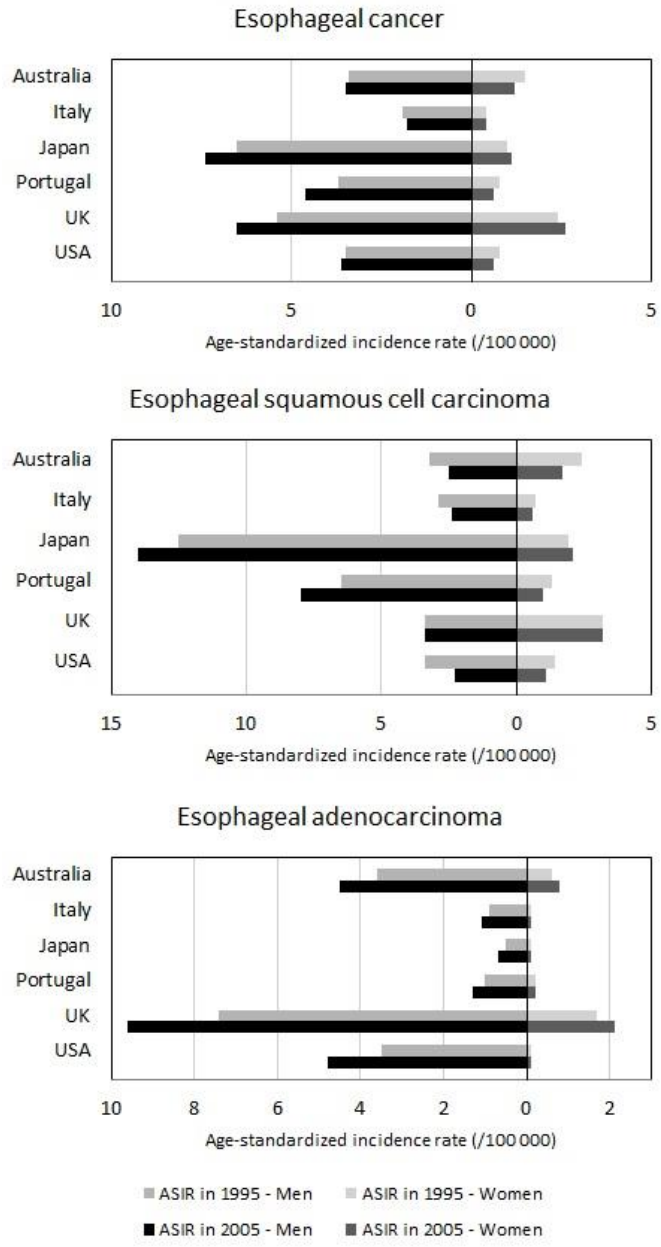
Data on the prevalence of exposure to risk factors were collected, by sex and age group (15-44, 45-54, 55-64, 65-74 and 75+), from the World Health Organization (WHO) Global Infobase[18], country-specific national health and nutrition surveys, and literature searches, for two time periods (1995 and 2005, minus the lag time considered for each determinant). When data was not available for the specific years of interest, we estimated the levels of exposure after a linear regression analysis using observed values for at least two other periods. Since data on the joint consumption of alcohol and tobacco are scarce and not usually evaluated in national health surveys, a single paper with representative data from the general population in each country was used to estimate the sex-specific proportion of alcohol drinkers among smokers; this proportion was assumed constant over time and it was applied to the prevalence of ever smokers and that of ever drinkers, as applicable, to yield estimates of separate and joint consumption. For *H. pylori* infection, we selected all population-based studies assessing the infection through serologic methods in each of the considered countries among those identified in a previous systematic review[19], and performed linear regression analyses to estimate the prevalence of exposure for the years of interest, by age group. Estimates of the levels of exposure in the adult population in each of the selected countries and the corresponding data sources are summarized in Supplemental Table 2; trends in the exposures to risk factors were very heterogeneous across countries, with various patterns being observed according to the risk factor and by sex.

Esophageal cancer incidence by subtype

Esophageal cancer incidence data were obtained from the Cancer Incidence in Five Continents online database, CI5-plus[20], for Australia, Italy, Japan, the UK and the USA; these countries were chosen to represent different ratios of the number of incident cases of the main histological types of esophageal cancer and a small proportion of cases of unspecified subtype, and to include distinct patterns of variation in ESCC and EAC incidence rates. Data from different cancer registries in these countries were aggregated to ensure the highest geographic coverage. For Portugal, data were retrieved from the North Region Cancer Registry, which covers approximately 30% of the national population and has reported the highest esophageal cancer incidence rates in the country[21].

The number of cases diagnosed in 1995 and 2005 in each country was estimated as the average of the 1994-1996 and 2004-2006 periods, respectively, to increase stability in the results. Data were collected by sex, age group (15-44, 45-54, 55-64, 65-74 and 75+ years) and histological type. Population figures for those periods were those presented by each cancer registry. The years 1995 and 2005 were chosen based on cancer data availability, as information provided by CI5-plus covers the years up to 2007.

Between 1995 and 2005, the esophageal cancer age-standardized (World standard population[22]) incidence rates (ASIR) increased for both sexes in Japan and the UK, while they increased among men and decreased among women in Australia, Portugal and the USA; in Italy, rates decreased among men and were stable among women. Patterns by subtype were very heterogeneous; for ESCC, Australia, Italy and the USA had decreasing ASIR for both sexes, Japan presented opposite trends, Portugal had increasing ASIR among men and decreasing among women, while the UK presented stable ASIR for both sexes. For EAC, ASIR increased in all settings among men, while among women they increased in Australia and the UK, but remained stable for other countries, with values below 0.5 per 100 000 (Figure 2).



UK: United Kingdom; USA: United States of America.

Figure 2: Age-standardized (World standard population) incidence rates (ASIR) per 100 000 of esophageal cancer in 1995 and 2005, by histological type, country and sex.

Calculation of the number of cases prevented (CP)

For continuous variables, namely BMI, and fruit, vegetable and red meat consumption, the number of CP was calculated as the product of three variables: the number of cases expected in 2005 (if 1995 rates persisted), the absolute reduction in the mean exposure between 1995 and 2005, and the regression coefficient quantifying the increase in risk of developing the disease by a unit increase in the exposure. For dichotomous variables, namely smoking, alcohol drinking and *H. pylori* infection, PAFs were calculated, for 1995 and 2005, as $(P\times(RR-1))/(1+P\times(RR-1))$, where P is the prevalence of the risk factor (in each year minus the lag time) and RR is the relative risk for that exposure. The number of CP was then estimated as the number of cases expected in 2005 if 1995 rates had persisted, multiplied by the difference between the PAFs in 2005 and that in 1995. Thus, CPs should be interpreted as the number of cases that were prevented (as compared to the number of cases expected had rates in 1995 persisted) due to variations in exposures to risk factors.

The numbers of CP as a result of risk factor changes were quantified for each histological type (ESCC and EAC), by sex and by age group (15-44, 45-54, 55-64, 65-74, 75+), to account for potential differences in effects across these strata. Estimates were then added to obtain CP at all ages, for ESCC and EAC (separately and combined), by sex.

Predictions for 2005

The number of cases predicted for 2005 by the model based on the trends in the exposure to risk factors (named henceforth the "risk factors' model") was estimated as the difference between the number of expected cases for 2005, had the 1995 rates persisted (named henceforth the "naive model"), and the number of CP. For each country, we computed the percent difference between the number of cases predicted by the models for 2005 and the ones observed, by sex and histological type; this reflects the deviation between the incident cases predicted by the models and those observed. When the number of predicted cases was lower than that of the observed cases, a negative value was presented for this proportion. We then compared the deviations obtained by the risk factors' model with those obtained by the naive model.

Precision of the estimates

We computed 95% credibility intervals for each estimate, through Monte Carlo simulation methods[23], by using 95% confidence intervals, when available, or ±20% otherwise, of both the prevalence of (for categorical variables) or mean (for continuous variables) exposures and the corresponding RR or regression coefficient, as applicable. We generated 1000 replicates assuming Normal distributions for the ln RR and for the regression coefficients.

RESULTS

Table 1 depicts the comparison between the subtype- and sex-specific numbers of cases observed in 2005 with the ones expected by the naive model, and the ones predicted by the risk factors' model. When combining the estimates for both subtypes, absolute deviations between the number of cases predicted and those observed in 2005 ranged between 1.8% (1220 predicted vs. 1242 observed, in Japan) and 23.6% (2293 vs. 3003, in the UK) among men, and between 0.0% (30 vs. 30, in Japan) and 18.0% (373 vs. 316, in Australia) among women. For ESCC, the deviations ranged between 1.0% in Japan and 22.5% in Portugal among men, and between 0.0% in Portugal and 25.3% in Australia among women; for EAC, corresponding values were 5.1% in Australia and 29.7% in Italy among men, and 0.0% in Portugal and 31.5% in the USA among women.

Table 1: Number of esophageal cancer cases observed, expected (had the 1995 rates persisted – "naive model") and predicted for 2005 (based on trends in the exposure to risk factors – "risk factors' model"), by subtype, country and sex.

	Cases observed 1995	Cases observed 2005	Cases expected 2005	Cases prevented (CP)	CP explained by model	Cases predicted 2005	95% credibility interval	% difference expected vs. observed	% difference predicted vs. observed
Esophageal cancer									
Australia									
Men	526	704	689	-15	-43	732	681 ; 801	-2.1	4.0
Women	295	316	373	57	0	373	351 ; 411	18.0	18.0
Italy									
Men	105	114	121	7	4	117	109 ; 123	6.1	2.6
Women	32	36	38	2	1	37	35 ; 41	5.6	2.8
Japan									
Men	830	1242	1099	-143	-121	1220	1158 ; 1332	-11.5	-1.8
Women	157	210	210	0	-5	215	205 ; 227	0.0	2.4
Portugal									
Men	96	141	115	-26	7	108	100 ; 117	-18.4	-23.4
Women	29	30	36	6	6	30	27 ; 33	20.0	0.0
UK									
Men	2017	3003	2476	-527	183	2293	2079 ; 2462	-17.5	-23.6
Women	1306	1618	1493	-125	84	1409	1285 ; 1490	-7.7	-12.9
USA									
Men	694	884	849	-35	87	762	724 ; 817	-4.0	-13.8
Women	256	278	297	19	23	274	253 ; 289	6.8	-1.4
ESCC									
Australia									
Men	247	256	324	68	17	307	277 ; 334	26.6	19.9
Women	232	221	293	72	16	277	254 ; 305	32.6	25.3
Italy									
Men	80	77	92	15	1	91	82 ; 95	19.5	18.2
Women	26	28	31	3	1	30	28 ; 34	10.7	7.1
Japan									
Men	799	1183	1057	-126	-114	1171	1110 ; 1283	-10.7	-1.0
Women	150	200	200	0	-3	203	194 ; 216	0.0	1.5
Portugal									
Men	82	120	99	-21	6	93	86 ; 101	-17.5	-22.5
Women	25	24	31	7	7	24	21 ; 27	29.2	0.0

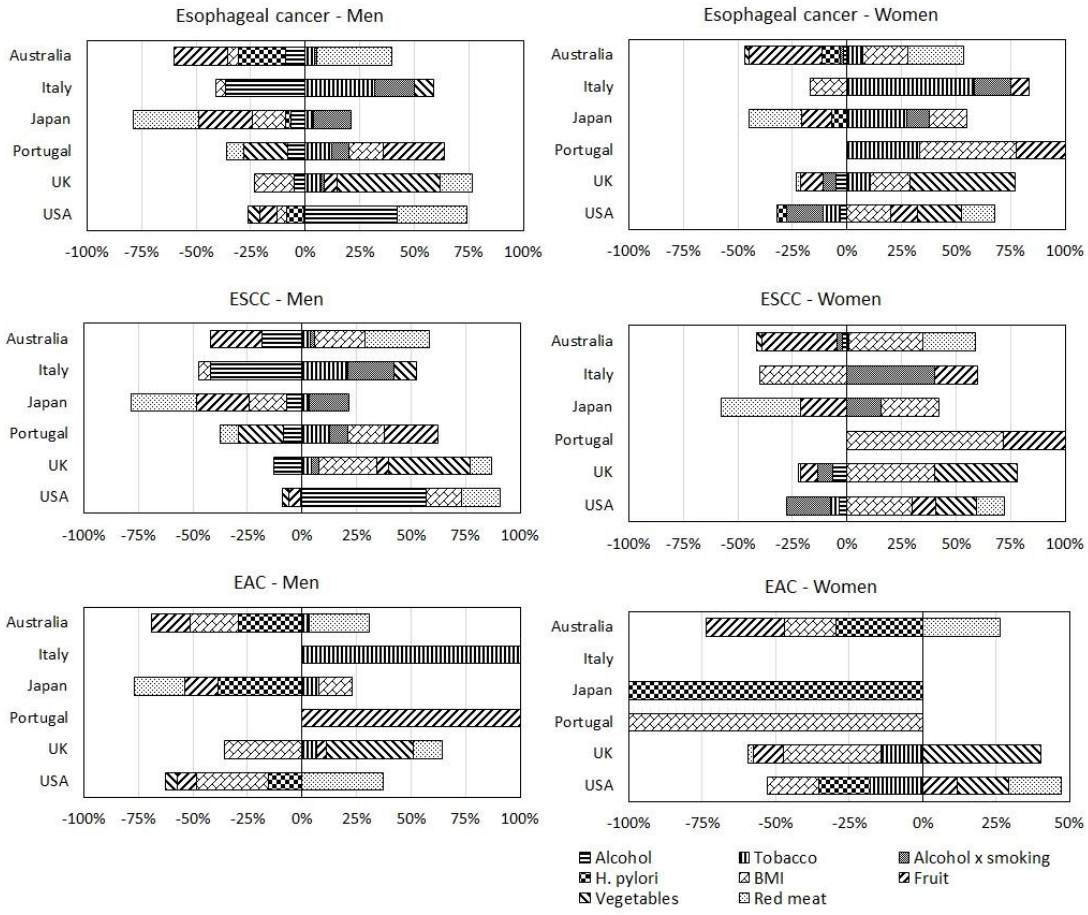
UK									
Men	643	784	791	7	103	688	625 ; 734	0.9	-12.2
Women	831	959	951	-8	103	848	766 ; 905	-0.8	-11.6
USA									
Men	339	285	415	130	110	305	278 ; 337	45.6	7.0
Women	191	167	222	55	24	198	180 ; 212	32.9	18.6
EAC									
Australia									
Men	279	448	365	-83	-60	425	383 ; 487	-18.5	-5.1
Women	63	95	80	-15	-16	96	87 ; 115	-15.8	1.1
Italy									
Men	25	37	29	-8	3	26	24 ; 30	-21.6	-29.7
Women	6	8	7	-1	0	7	6 ; 8	-12.5	-12.5
Japan									
Men	31	59	42	-17	-7	49	41 ; 60	-28.8	-16.9
Women	7	10	10	0	-2	12	9 ; 14	0.0	20.0
Portugal									
Men	14	21	16	-5	1	15	12 ; 19	-23.8	-28.6
Women	4	6	5	-1	-1	6	4 ; 7	-16.7	0.0
UK									
Men	1374	2219	1685	-534	80	1605	1400 ; 1766	-24.1	-27.7
Women	475	659	542	-117	-19	561	483 ; 622	-17.8	-14.9
USA									
Men	355	599	434	-165	-23	457	428 ; 500	-27.5	-23.7
Women	65	111	75	-36	-1	76	68 ; 84	-32.4	-31.5

ESCC: Esophageal squamous cell carcinoma; EAC: Esophageal adenocarcinoma, UK: United Kingdom; USA: United States of America.

In Australia, in analyses performed by subtype and by sex the risk factors' model showed lower deviations from what was observed in 2005 than the naive model; when combining both subtypes, the differences between the two models were attenuated (Table 1). In Italy, for ESCC, the risk factors' model had a better performance than the naive model, but not for EAC. In Japan, the risk factors' model presented lower deviations from what was observed, except for EAC among women, who presented a much lower number of incident cases. In Italy and Japan, when considering both subtypes combined, the risk factors' model yielded deviations that did not exceed 3%. In Portugal, the cases estimated by the risk factors' model were closer to the observed among women, but not among men. Globally, the worst performance of the risk factors' model was found in the UK, where the risk factors' model only presented a lower deviation than the naive model (14.9% vs. 17.8%) for EAC among women. For the USA, the risk factors' model performed better than the naive model when considering each subtype separately, although the differences between the observed and the predicted number of cases were still high, especially for EAC (23.7% among men, 31.5% among women); for both subtypes combined, the risk factors' model had lower deviations than the naive among women (1.4% vs. 6.8%), but not among men (13.8% vs. 4.0%).

In Japan, the credibility intervals obtained for predictions using the risk factors' model always included the number of cases observed in 2005, while the opposite was verified in the UK (Table 1). In the remaining countries, when considering subtype-specific data, the credibility intervals did not always include the number of cases observed in 2005.

The contribution of each risk factor to the number of CP explained by the model varied widely between countries, sexes and cancer subtypes (Figure 3, Supplemental Tables 3 and 4). For both subtypes combined, CP explained by the model were mainly influenced by changes in the mean daily intake of fruits (24% in Australia and Japan, 28% in Portugal) and red meat (35% in Australia, 30% in Japan, 32% in the USA), among men, and in mean BMI (from 17% in Italy and Japan to 44% in Portugal), among women. For ESCC, the largest contributors to the number of CP explained were mean daily fruit and red meat intake among men and mean BMI among women, though among Italian men the separate and joint consumption of alcohol and tobacco accounted for 84% of CP explained by the model for ESCC. For EAC, the most relevant changes in exposures were related to *H. pylori* infection in both sexes, red meat intake among men and BMI among women. Due to the much lower incidence of EAC than that of ESCC in Italy, Japan and Portugal, very few cases were explained by the risk factors' model. In Italy, the number of CP was -1 and the model yielded no variations in EAC due to changes in the exposure to risk factors among women. In Portugal, the model predicted a decrease of one EAC case among men due to an increasing consumption of fruits, and an increase in the same amount among women due to the increasing mean BMI.



ESCC: Esophageal squamous cell carcinoma; EAC: Esophageal adenocarcinoma; UK: United Kingdom; USA: United States of America *H. pylori*: *Helicobacter pylori*; BMI: Body mass index.

Figure 3: Proportion of cases prevented between 1995 and 2005 due to changes in the exposure to risk factors, by cancer subtype and by sex.

DISCUSSION

This study quantified the contribution of a comprehensive set of risk factors to the observed changes in esophageal cancer incidence, by adapting the methods used by the IMPACT model. In general, the proposed model yielded closer predictions to the observed number of cases than the naive assumption of constant rates over the years, which is relevant, since the latter will always have a good fit when the rates remain relatively constant. Nearly half of the sex- and histological type-specific predictions of the risk factors' model had a 95% credibility interval including the observed number of cases, regardless of the patterns of variation in esophageal cancer incidence. The performance of the model was consistently better for Japan, and worse for the UK.

The ability of a model to explain cancer incidence trends and to perform predictions depends on the extent to which its underlying assumptions are met. The understanding of the etiology of multifactorial conditions and the accurate quantification of the relation between the different risk factors and the disease of interest is essential. In the present study, we assessed the current knowledge on the etiology of esophageal cancer, using several systematic reviews and meta-analyses to accurately quantify the association between each risk factor and the occurrence of esophageal cancer's major histological types. The use of RR estimates specific by geographical area, sex and histological type is expected to have contributed to improve the fit of the proposed model. An example is the use of very different RR estimates for Japan and the other countries regarding the separate and joint consumption of alcohol and tobacco; alcohol consumption in Asia is much lower than that in Western countries[24], and therefore the lower RR estimates from Asian populations[25] hindered an overestimation of prevented cases between 1995 and 2005 due to these risk factors, which ultimately led to a good model fit in that country. For red meat consumption, a more recent meta-analysis than the one we used reported separate RR estimates according to geographical area, yielding a higher risk of ESCC in Europe than in Asia, and a higher risk of EAC in the USA than in Europe[26]; however, these estimates could not be used in our model since they did not report the change in risk due to increases/decreases in consumption, but rather the comparison between the highest and lowest categories of exposure. Processed meat has been increasingly mentioned as a risk factor for esophageal cancer, with meta-analyses suggesting a higher risk of ESCC with its consumption than the one observed for red meat[27, 28]. In the present study, this risk factor could not be included since data on daily per capita consumption is not routinely collected in national health surveys and there is no proxy data such as availability from the Food and Agriculture Organization balance sheets[29]. However, part of its effect is likely included in the results obtained for red meat and the inclusion of both risk factors would probably yield an overestimation of cases attributable to these risk factors. A relevant risk factor for EAC that could not be considered in the model was GERD. Data on the exposure to GERD were scarce and methodologically heterogeneous, mainly because of the multiplicity of definitions across studies. Even though some systematic reviews have been performed on the prevalence of GERD, aiming to describe worldwide trends

on this exposure[30, 31], there were few population-based studies, and even fewer reported prevalence based on the same definition. Furthermore, as studies included in those reviews were mainly performed since the 1990's and changes in GERD-related therapies have been observed in more recent years[32, 33], current exposure trends might not allow a reasonably accurate estimation of the levels of exposure in the period relevant for this study. Nevertheless, although the variation in the frequency of GERD cannot be accurately quantified, an increase could be expected[30], which would have contributed for a greater number of cases of EAC, and therefore a better fit of the model in most countries.

In addition to the knowledge on cancer etiology, the performance of a prediction method relies heavily on the quality of the data included in the analyses. The quality of information regarding the exposure to risk factors is crucial and was probably the most important determinant of the yielding of the risk factors' model. As we selected several countries with different patterns of incidence trends regarding esophageal cancer's major histological types, they also show various trends of exposure to risk factors. When data on exposure to a risk factor could not be obtained for the years of interest, we used linear regression analyses with other periods of observation, which may have led to bias in the estimated CP since the observed changes in more recent years may not have been verified in the past. The direction of this bias is not straightforward as it depends on the risk factor, varying across countries and between sexes. An assumption of a linear trend in the period of analysis is also needed[15]. Finally, as cancer onset is preceded by an often long latency period, which is imprecisely estimated, the observed changes in exposures to risk factors in a 10-year period may not suffice to be reflected in cancer incidence estimates, which further compromises the yielding of the model.

When the risk factors' model yielded better predictions for 2005 than the naive model, the changes in risk factors that most contributed to changes in incidence were mean BMI, and red meat and fruit intake for ESCC, and the prevalence of *H. pylori* and mean BMI for EAC. For ESCC, this may seem surprising given that alcohol drinking and tobacco smoking are commonly referred to as the most relevant risk factors of ESCC, with more than 90% of ESCC cases being attributed to these risk factors in some Western countries[5]. However, our results were consistent with these values, with PAFs among men regarding the interaction between drinking and smoking in 2005 ranging between 80.6% in Portugal and 90.1% in the UK (values not shown). Since there were no large differences in PAFs between 1995 and 2005, the contribution of alcohol and tobacco to changes in incidence in that period was smaller than that of the aforementioned risk factors in most settings.

Regarding the outcomes considered in this study, namely the number of incident cases of esophageal cancer by subtype, data for most countries were derived from CI5-plus[20]. This database aggregates annual data from selected cancer registries included in consecutive CI5 publications to allow for time trends analyses using high-quality information. For Portugal, data was retrieved from the North Region Cancer Registry; although data from this registry are not available in CI5-plus, they were included in CI5-IX[34], which covers the period 1998-2002, a

similar time frame to the one used in the present study, ensuring the quality of the data used. Furthermore, with the exception of Japan, where the proportion of cases of unspecified subtype (20.7% in 1994-1996, 15.5% in 2004-2006) was above that of EAC (2.9% in 1994-1996, 3.8% in 2004-2006), a low proportion of unspecified cases was observed in all countries, regardless of the predominant subtype in each setting. Nevertheless, the potential misclassification of gastric cardia tumors for EAC, which may have contributed to the increase in EAC rates observed in some countries[35], cannot be ignored, as it may lead to a spuriously higher difference between the observed and expected cases of EAC for 2005 and, ultimately, to a spuriously poor performance in some settings. This may be an explanation for the greater deviations between the number of predicted and observed cases in the UK, as cardia cancer cases comprise the majority of gastric tumors of specified location in the country[36].

This study adds to previous research on this topic a framework for analysis of the contribution of the variation in the exposure to different factors known to be associated with esophageal cancer, as well as for long-term predictions of ESCC and EAC at a population level.

Nearly half of the strata-specific predictions of the risk factors' model had a 95% credibility interval including the observed number of cases, regardless of the patterns of variation in esophageal cancer incidence. These results show the potential of this model for the planning of interventions and to define cancer control policies, but future studies, taking into account a wider period of time between exposure assessments, while also using more accurate estimates of the variation in the exposure to the risk factors, are expected to improve the accuracy of the predictions.

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The authors declare no conflicts of interest.

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Supplemental Table 1: Relative risk (RR) estimates, corresponding 95% confidence intervals (95%CI) and lag times for the association between risk factors and incidence of esophageal cancer, by histological type.

Outcome	Risk factor	Lag time (years)	Categories of exposure	Subgroup	RR	95%CI	Source of information on RR (author, year)
ESCC	Alcohol	15	Ever drinkers and never smokers vs. never drinkers and never smokers	Men (non-Asian)	4.03	1.76-9.21	Castelsague, 1999[37]
				Women (non-Asian)	1.42	0.82-2.48	Castelsague, 1999[37]
				Asian	1.21	0.81-1.81	Prabhu, 2014[25]
	Tobacco	20	Ever smokers and never drinkers vs. never smokers and never drinkers	Men (non-Asian)	4.45	2.09-9.47	Castelsague, 1999[37]
				Women (non-Asian)	1.57	0.89-2.75	Castelsague, 1999[37]
				Asian	1.36	1.14-1.61	Prabhu, 2014[25]
	Alcohol x smoking	15	Ever drinkers and ever smokers vs. never drinkers and never smokers	Men (non-Asian)	17.00	8.36-34.78	Castelsague, 1999[37]
				Women (non-Asian)	7.26	3.68-14.33	Castelsague, 1999[37]
				Asian	3.28	2.11-5.08	Prabhu, 2014[25]
	Body mass index	10	Increasing risk per 5 kg/m^2	Men	0.71	0.60-0.85	Renehan, 2008[8]
				Women	0.57	0.47-0.69	Renehan, 2008[8]
	Red meat consumption	10	Per 100g/day increase	Overall	1.41	1.16-1.70	Qu, 2013[93]
EAC	*H. pylori* infection	20	Infected vs. non-infected	Overall	0.57	0.44-0.73	Nie, 2014[38]
	Tobacco	20	Ever vs. never smokers	Men	2.10	1.71-2.59	Cook, 2010[39]
			Ever vs. never smokers	Women	1.74	1.21-2.51	Cook, 2010[39]
	Body mass index	10	Per 5 kg/m^2 increase	Men	1.52	1.33-1.74	Renehan, 2008[8]
				Women	1.51	1.31-1.74	Renehan, 2008[8]
	Red meat consumption	10	Per 100g/day increase	Overall	1.45	1.09-1.93	Huang, 2013[40]
Esophageal cancer (irrespective of subtype)	Fruit consumption	15	Per 100g/day increase	Overall	0.72	0.62-0.83	Riboli, 2003[17]
				Asia	0.68	0.43-1.06	Riboli, 2003[17]
				Europe	0.82	0.66-1.01	Riboli, 2003[17]
				USA	0.80	0.67-0.96	Riboli, 2003[17]
	Vegetable consumption	15	Per 100g/day increase	Overall	0.89	0.82-0.97	Riboli, 2003[17]
				Asia	0.98	0.91-1.05	Riboli, 2003[17]
				Europe	0.79	0.68-0.92	Riboli, 2003[17]
				USA	0.81	0.67-0.98	Riboli, 2003[17]

ESCC: Esophageal squamous cell carcinoma; EAC: Esophageal adenocarcinoma; *H. pylori* : *Helicobacter pylori*; USA: United States of America.

Supplemental Table 2: Estimates of exposure to risk factors, in 1995 and 2005 minus the lag times considered for each risk factor, by country and sex, in individuals aged 15 years or over.

	Men		Women		Sources of data
	1995-lag	2005-lag	1995-lag	2005-lag	
Australia					
Prevalence of ever drinkers and never smokers, %	44.7	45.2	53.9	55.3	[41, 42]
Prevalence of ever smokers and never drinkers, %	8.6	8.5	13.9	13.4	[41, 42]
Prevalence of ever drinkers and ever smokers, %	48.5	48.2	31.8	30.6	[41]
Prevalence of ever smokers, %	57.2	56.8	46.2	44.6	[42]
Prevalence of *Helicobacter pylori* infection, %	60.8	45.8	60.8	45.8	[19]
Mean body mass index, kg/m^2	25.0	26.1	23.9	25.3	[43, 44]∗
Mean fruit intake, g/d	175.9	158.2	206.5	157.6	[45]
Mean vegetable intake, g/d	299.3	289.2	242.9	233.1	[45]
Mean red meat intake, g/d	105.1	73	63.9	37.0	[46]
Italy					
Prevalence of ever drinkers and never smokers, %	30.1	38.2	56.9	54.5	[47-50]
Prevalence of ever smokers and never drinkers, %	5.7	4.5	5.2	5.6	[47, 51-53]∗
Prevalence of ever drinkers and ever smokers, %	46.5	37.6	12.5	13.1	[47]
Prevalence of ever smokers, %	56.6	44.7	17.3	18.5	[51-53]∗
Prevalence of *Helicobacter pylori* infection, %	50.3	46.1	50.3	46.1	[19]
Mean body mass index, kg/m^2	26.0	26.4	26.3	25.6	[53, 54]∗
Mean fruit intake, g/d	201.4	200.1	164.9	185.7	[55, 56]
Mean vegetable intake, g/d	209.9	219.2	219.7	217.4	[55, 56]
Mean red meat intake, g/d	68.0	66.0	59.0	55.0	[55, 56]
Japan					
Prevalence of ever drinkers and never smokers, %	10.1	11.8	1.3	2.8	[57, 58]∗
Prevalence of ever smokers and never drinkers, %	15.6	14.6	4.1	5.5	[57, 58]∗
Prevalence of ever drinkers and ever smokers, %	45.2	42.2	3.2	4.1	[57]
Prevalence of ever smokers, %	62.3	58.2	6.9	9.1	[58]∗
Prevalence of *Helicobacter pylori* infection, %	76.2	65.2	76.2	65.2	[19]†
Mean body mass index, kg/m^2	22.9	23.1	22.6	22.4	[59]
Mean fruit intake, g/d	133.2	116.3	163.3	146.2	[60]
Mean vegetable intake, g/d	323.6	307.5	289.3	283.1	[60]
Mean red meat intake, g/d	46.5	57.2	27.3	36.7	[60]
Portugal					
Prevalence of ever drinkers and never smokers, %	53.4	55.7	51.3	52.5	[61-64]
Prevalence of ever smokers and never drinkers, %	11.8	10.9	1.1	3.3	[61-67]
Prevalence of ever drinkers and ever smokers, %	34.1	31.5	1.4	3.1	[61]
Prevalence of ever smokers, %	49.3	44.9	4.2	6.9	[62-67]
Prevalence of *Helicobacter pylori* infection, %	80.1	78.5	80.1	78.5	[19]†
Mean body mass index, kg/m^2	25.0	25.4	23.9	24.7	[62-64]
Mean fruit intake, g/d	209.1	230.6	246.1	270.7	[68, 69]
Mean vegetable intake, g/d	421.8	396.3	418.8	404.4	[68, 69]
Mean red meat intake, g/d	69.8	77.3	57.8	63.7	[68, 69]
UK					
Prevalence of ever drinkers and never smokers, %	51.6	56.3	56.8	61.9	[70, 71]
Prevalence of ever smokers and never drinkers, %	7.7	6.5	19.2	17.6	[70, 71]
Prevalence of ever drinkers and ever smokers, %	63.2	54.8	36.4	34.1	[70]
Prevalence of ever smokers, %	76.8	65.4	53.9	50.4	[71]
Prevalence of *Helicobacter pylori* infection, %	46.2	46.1	46.2	46.1	[19]†
Mean body mass index, kg/m^2	25.1	25.6	24.7	25.6	[72, 73]∗
Mean fruit intake, g/d	103.9	103.4	107.4	108.6	[74, 75]
Mean vegetable intake, g/d	73.1	110.1	55.5	97.7	[74, 75]
Mean red meat intake, g/d	86.7	85.7	43.1	48.1	[74, 75]
USA					
Prevalence of ever drinkers and never smokers, %	31.3	27.6	16.5	22.5	[76-78]
Prevalence of ever smokers and never drinkers, %	7.0	6.4	13.7	13.7	[76, 79, 80]
Prevalence of ever drinkers and ever smokers, %	60.2	54.5	32.1	31.9	[76]
Prevalence of ever smokers, %	70.0	63.7	45.8	45.7	[79, 80]
Prevalence of *Helicobacter pylori* infection, %	44.0	39.3	44.0	39.3	[19]†

Mean body mass index, kg/m^2	26.3	26.9	26.1	26.9	[81]*
Mean fruit intake, g/d	200.2	190.3	113.1	134.9	[82]
Mean vegetable intake, g/d	360.5	326.7	281.4	262.4	[83]
Mean red meat intake, g/d	100.0	83.3	57.5	46.9	[84]

UK: United Kingdom; USA: United States of America.

* Data retrieved from the World Health Organization Global Infobase[18].

† Exposure for the year of interest estimated through regression analyses.

Supplemental Table 3: Number of esophageal cancer cases prevented (n) between 1995 and 2005 due to changes in the exposure to risk factors, and corresponding 95% credibility intervals (CI), by histological type, among men.

	Australia n (95%CI)	Italy n (95%CI)	Japan n (95%CI)	Portugal n (95%CI)	UK n (95%CI)	USA n (95%CI)
Esophageal cancer						
Prevalence of ever drinkers and never smokers	-19	-8	-14	-2	-18	76
	(-29 ; -6)	(-10 ; -3)	(-41 ; 4)	(-5 ; 1)	(-44 ; 8)	(46 ; 92)
Prevalence of ever smokers and never drinkers	4	4	7	3	6	-1
	(-6 ; 14)	(2 ; 7)	(-2 ; 14)	(0 ; 5)	(-17 ; 26)	(-11 ; 9)
Prevalence of ever drinkers and ever smokers	2	4	36	2	5	0
	(-3 ; 6)	(2 ; 7)	(-3 ; 76)	(0 ; 5)	(-4 ; 16)	(-5 ; 5)
Prevalence of ever smokers	5	3	1	0	19	0
	(-9 ; 17)	(1 ; 4)	(-1 ; 3)	(0 ; 1)	(-43 ; 85)	(-16 ; 15)
Prevalence of *H. pylori* infection	-46	0	-5	0	0	-14
	(-95 ; -11)	(-3 ; 1)	(-15 ; 2)	(-3 ; 3)	(-135 ; 143)	(-43 ; 11)
Mean body mass index	-11	-1	-32	4	-63	-8
	(-23 ; 3)	(-1 ; 1)	(-74 ; 3)	(3 ; 7)	(-111 ; -24)	(-18 ; 2)
Mean fruit intake	-52	0	-51	7	20	-15
	(-84 ; -34)	(-3 ; 3)	(-113 ; 0)	(3 ; 12)	(-32 ; 83)	(-32 ; -2)
Mean vegetable intake	0	2	0	-5	163	-9
	(-3 ; 9)	(0 ; 5)	(-11 ; 7)	(-9 ; -3)	(136 ; 256)	(-18 ; -2)
Mean red meat intake	74	0	-63	-2	51	58
	(55 ; 93)	(0 ; 2)	(-96 ; -49)	(-4 ; -1)	(22 ; 80)	(44 ; 76)
ESCC						
Prevalence of ever drinkers and never smokers	-19	-8	-14	-2	-18	76
	(-29 ; -6)	(-10 ; -3)	(-41 ; 4)	(-5 ; 1)	(-44 ; 8)	(46 ; 92)
Prevalence of ever smokers and never drinkers	4	4	7	3	6	-1
	(-6 ; 14)	(2 ; 7)	(-2 ; 14)	(0 ; 5)	(-17 ; 26)	(-11 ; 9)
Prevalence of ever drinkers and ever smokers	2	4	36	2	5	0
	(-3 ; 6)	(2 ; 7)	(-3 ; 76)	(0 ; 5)	(-4 ; 16)	(-5 ; 5)
Mean body mass index	24	-1	-34	4	37	22
	(16 ; 33)	(-1 ; 1)	(-75 ; 2)	(3 ; 7)	(22 ; 54)	(15 ; 29)
Mean fruit intake	-24	0	-49	6	7	-7
	(-45 ; -12)	(-3 ; 3)	(-112 ; 1)	(2 ; 11)	(-17 ; 32)	(-19 ; 1)
Mean vegetable intake	0	2	0	-5	52	-4
	(-2 ; 5)	(0 ; 4)	(-11 ; 7)	(-9 ; -2)	(36 ; 87)	(-10 ; 1)
Mean red meat intake	30	0	-60	-2	14	24
	(24 ; 44)	(0 ; 2)	(-93 ; -47)	(-4 ; -1)	(7 ; 26)	(20 ; 37)
EAC						
Prevalence of ever smokers	5	3	1	0	19	0
	(-9 ; 17)	(1 ; 4)	(-1 ; 3)	(0 ; 1)	(-43 ; 85)	(-16 ; 15)
Prevalence of *H. pylori* infection	-46	0	-5	0	0	-14
	(-95 ; -11)	(-3 ; 1)	(-15 ; 2)	(-3 ; 3)	(-135 ; 143)	(-43 ; 11)
Mean body mass index	-35	0	2	0	-100	-30
	(-45 ; -25)	(0 ; 0)	(0 ; 3)	(-1 ; 0)	(-142 ; -64)	(-37 ; -23)
Mean fruit intake	-28	0	-2	1	13	-8
	(-49 ; -13)	(-1 ; 1)	(-4 ; 0)	(0 ; 2)	(-33 ; 74)	(-20 ; 2)
Mean vegetable intake	0	0	0	0	111	-5
	(-3 ; 6)	(0 ; 1)	(0 ; 0)	(-1 ; 0)	(81 ; 190)	(-11 ; 0)
Mean red meat intake	44	0	-3	0	37	34
	(25 ; 56)	(0 ; 0)	(-4 ; -1)	(0 ; 0)	(9 ; 64)	(19 ; 44)

ESCC: Esophageal squamous cell carcinoma; EAC: Esophageal adenocarcinoma; *H. pylori*: *Helicobacter pylori*; UK: United Kingdom; USA: United States of America.

Supplemental Table 4: Number of esophageal cancer cases prevented (n) between 1995 and 2005 due to changes in the exposure to risk factors, and corresponding 95% credibility intervals (CI), by histological type, among women.

	Australia n (95%CI)	Italy n (95%CI)	Japan n (95%CI)	Portugal n (95%CI)	UK n (95%CI)	USA n (95%CI)
Esophageal cancer						
Prevalence of ever drinkers and never smokers	-2 (-10 ; 6)	0 (-1 ; 1)	0 (0 ; 0)	0 (-2 ; 0)	-12 (-37 ; 12)	-2 (-5 ; 2)
Prevalence of ever smokers and never drinkers	1 (-4 ; 4)	0 (0 ; 0)	0 (0 ; 1)	0 (0 ; 0)	0 (-16 ; 14)	-2 (-6 ; 1)
Prevalence of ever drinkers and ever smokers	-2 (-13 ; 10)	2 (0 ; 3)	3 (-1 ; 4)	0 (0 ; 0)	-13 (-47 ; 22)	-11 (-18 ; -3)
Prevalence of ever smokers	0 (-3 ; 3)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	-14 (-32 ; 5)	-3 (-5 ; -1)
Prevalence of *H. pylori* infection	-10 (-24 ; -1)	0 (-1 ; 0)	-2 (-4 ; 1)	0 (-1 ; 1)	0 (-61 ; 67)	-3 (-9 ; 3)
Mean body mass index	25 (14 ; 36)	-2 (-4 ; -2)	5 (1 ; 7)	4 (3 ; 6)	41 (5 ; 78)	13 (6 ; 16)
Mean fruit intake	-41 (-63 ; -30)	1 (0 ; 3)	-4 (-14 ; 6)	2 (0 ; 3)	-24 (-61 ; 4)	8 (4 ; 16)
Mean vegetable intake	-2 (-8 ; 0)	0 (-1 ; 1)	0 (-1 ; 2)	0 (0 ; 1)	110 (89 ; 166)	13 (1 ; 25)
Mean red meat intake	31 (23 ; 42)	0 (0 ; 0)	-7 (-11 ; -5)	0 (0 ; 0)	-4 (-14 ; 4)	10 (8 ; 14)
ESCC						
Prevalence of ever drinkers and never smokers	-2 (-10 ; 6)	0 (-1 ; 1)	0 (0 ; 0)	0 (-2 ; 0)	-12 (-37 ; 12)	-2 (-5 ; 2)
Prevalence of ever smokers and never drinkers	1 (-4 ; 4)	0 (0 ; 0)	0 (0 ; 1)	0 (0 ; 0)	0 (-16 ; 14)	-2 (-6 ; 1)
Prevalence of ever drinkers and ever smokers	-2 (-13 ; 10)	2 (0 ; 3)	3 (-1 ; 4)	0 (0 ; 0)	-13 (-47 ; 22)	-11 (-18 ; -3)
Mean body mass index	31 (20 ; 42)	-2 (-4 ; -2)	5 (1 ; 7)	5 (4 ; 7)	74 (44 ; 107)	16 (10 ; 19)
Mean fruit intake	-32 (-53 ; -21)	1 (0 ; 2)	-4 (-13 ; 6)	2 (0 ; 3)	-14 (-45 ; 7)	6 (2 ; 14)
Mean vegetable intake	-2 (-8 ; 0)	0 (-1 ; 1)	0 (-1 ; 2)	0 (0 ; 1)	70 (51 ; 114)	10 (-1 ; 21)
Mean red meat intake	22 (16 ; 34)	0 (0 ; 0)	-7 (-11 ; -5)	0 (0 ; 0)	-2 (-11 ; 3)	7 (5 ; 11)
EAC						
Prevalence of ever smokers	0 (-3 ; 3)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	-14 (-32 ; 5)	-3 (-5 ; -1)
Prevalence of *H. pylori* infection	-10 (-24 ; -1)	0 (-1 ; 0)	-2 (-4 ; 1)	0 (-1 ; 1)	0 (-61 ; 67)	-3 (-9 ; 3)
Mean body mass index	-6 (-9 ; -4)	0 (0 ; 0)	0 (0 ; 0)	-1 (-1 ; 0)	-33 (-53 ; -17)	-3 (-5 ; -2)
Mean fruit intake	-9 (-15 ; -5)	0 (0 ; 1)	0 (0 ; 1)	0 (0 ; 1)	-10 (-33 ; 5)	2 (0 ; 4)
Mean vegetable intake	0 (-2 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	40 (25 ; 69)	3 (-1 ; 6)
Mean red meat intake	9 (3 ; 11)	0 (0 ; 0)	0 (-1 ; 0)	0 (0 ; 0)	-2 (-6 ; 5)	3 (1 ; 4)

ESCC: Esophageal squamous cell carcinoma; EAC: Esophageal adenocarcinoma; *H. pylori*: *Helicobacter pylori*; UK: United Kingdom; USA: United States of America.

GENERAL DISCUSSION

Decision making towards cancer prevention and control requires monitoring of trends in cancer incidence and accurate estimation of its burden in different settings. This thesis aimed at the development of a model able to describe and predict esophageal cancer incidence, so that it could be used in countries with various incidence patterns and trends regarding its major subtypes, ESCC and EAC. The proposed model, to explain the past and to predict the future variations in esophageal cancer incidence relied on an extensive and detailed collection of data, from numerous sources.

We started by describing esophageal cancer incidence in different countries, in order to perceive the diversity in trends across different contexts, which should be taken into consideration in the development of the model (Papers I-III). Very different patterns by cancer subtype were observed among the selected countries and between sexes. In Northern Europe, EAC ASIR rose substantially among men and surpassed ESCC, similarly to what had been observed in the USA and Australia[125], whereas among women ESCC remained the predominant histological type. Northern Portugal presented slight increases in ASIR among men and a downward trend among women, mostly reflecting the trends in the incidence of ESCC, which is the major histological type in the region for both sexes.

In Europe, ESCC rates followed the trends in alcohol consumption, decreasing in southern countries and stabilizing in northern countries, while EAC followed more consistently the trends in overweight/obesity, with more appreciable increases in northern Europe than in southern countries. Thus, the limitation of one of these factors could lead to the avoidance of a substantial proportion of cases at a population level.

In order to accommodate the current knowledge on the etiology of esophageal cancer in the model to be developed and to take into account the variations in exposure to risk factors such as alcohol consumption or excess BMI, an accurate assessment of the strength of association between each risk factor and the occurrence of esophageal cancer had to be performed. We then conducted a systematic review of published meta-analyses on the associations between the major risk factors for esophageal cancer subtypes (Paper IV), which allowed for the description of existing studies in a standardized format, facilitating the selection of the most adequate RR estimates to use in the risk factors' model.

Prediction models heavily rely on the quality of information used, either regarding the exposures or the outcomes. In this thesis, we used information on cancer incidence from high-quality registries, which complied with quality requirements from the CI5 publications. For Portugal, data was retrieved from the RORENO; although data from this registry are not available in CI5-plus, they were included in CI5-IX[116], which covers the period 1998-2002, a similar time frame to the one used in the present study, ensuring the quality of the data used. However, some limitations in data collected must be discussed, namely regarding esophageal cancer subtypes. The increasing awareness of EAC may have led to the increase in its incidence rates, through misclassification of gastric cardia cancers[81]. Since data on gastric cancer sub-locations is not available from CI5-plus, we assessed CI5-X to inspect the proportions of gastric cancer by subtype in each of the countries considered for the development of the risk factors' model, namely Australia, Italy, Japan, the UK and the USA. In these settings, the proportion of gastric cancer cases of unspecified location often exceeded 30% and was higher than that observed for cardia cancer. In Northern Portugal, the proportion of unspecified cases was also higher than that observed for cardia and non-cardia cancers (Paper III). Therefore, and although the proportion of esophageal cancer cases of unspecified morphology was globally low in the countries considered, the extent to which the misclassification of cardia for EAC may have influenced EAC incidence trends could not be accurately quantified.

Regarding methodological issues of the applied methods, an important matter relates to the number of cases included in analyses. While the DH models are usually based on at least six consecutive years of data with 50 cases/deaths (all ages) recorded per year[90], the naive and the risk factors' models do not present a clear requirement on sample size. However, cancers presenting a low number of cases are also more prone to random variations, increasing the potential for deviations between the observed and the predicted incidence using either of these models. To attenuate the effect of random variations in predictions and increase stability in results provided by the latter methods, in Paper V we estimated the number of cases diagnosed in the years of interest (1995 and 2005) as the average of 3-year periods.

As esophageal cancer presents much smaller numbers of cases than other tumors, more stable estimates using our proposed methodology may be obtained for other outcomes. Also, our model heavily relies on accuracy of the estimates on the levels of exposure to several risk factors, which varies widely with time and across countries. In fact, this was probably the most important determinant of the deviations between predicted and observed values in some settings. A series of surveys on nationally representative samples of the population would constitute the ideal basis for the collection of these data (Papers III and V). However, for most distant years, the process of accessing information from such surveys or similar sources of information is very time-consuming and, sometimes, unsuccessful, either because the data were not collected for the risk factor of interest on given years, or the level of detail provided was insufficient to allow for a good performance of the model, or data collected in two different periods were not comparable due to changes in coding or questions asked to participants. This was one of the

major difficulties observed for alcohol consumption, for instance, since different surveys in the same country often measured consumption differently (e.g., prevalence of consumption in the month/year before the survey, number of drinks consumed per day/week). The major limitation in data collection was, however, observed for GERD. Data on exposure to GERD were scarce and very heterogeneous, mainly because of the multiplicity of definitions across studies. Even though some systematic reviews have been performed on the prevalence of GERD, aiming to describe worldwide trends on this exposure[126, 127], few population-based studies were found allowing for this comparison, and fewer reported prevalence based on the same definition, not allowing for an accurate quantification of the variation in the prevalence of this condition. Since most studies focusing on this determinant were conducted since the 1990's and changes in GERD-related therapies have been observed since then[128, 129], using recent exposure trends might yield contradicting results to the increasing trends expected for this risk factor in past decades. The non-inclusion of this risk factor is a likely explanation for the poor performance of the risk factors' model for EAC in some settings.

The performance of the proposed model varied widely across countries and between sexes, with no evident association with the patterns of trends observed in different settings. Globally, the proposed model yielded predictions closer to the observed number of cases than the naive assumption of constant rates from the past. As expected, the naive model presented lower deviations from the reality when no relevant variations in incidence trends were observed over time, while the risk factors' model provided better estimates in the other situations. On account of this limitation of the naive model, the advantage of using the risk factors' model may be further increased when considering longer-term predictions, since in these cases an assumption of constant rates is unlikely for most cancers and, in particular, for esophageal tumors.

To test this hypothesis, and in order to allow for comparisons between the three prediction methods used in the course of this work (DH, naive and risk factors' models), we predicted the number of incident cases in Northern Portugal for the years 2010 and 2020, at ages 15 years and older. For the DH model, we used data on incidence trends observed up to 2000 and 2009, respectively. For the other two models, we used the years 2000 and 2009, respectively, as the basis to perform predictions. The comparison between the three models for the year 2010 is presented in Table 3.

Using the three models to perform predictions for 2010, the last year with available data from RORENO, the closest results to the values observed in 2010 were yielded by the risk factors' model, with deviations of 1.1% among men and 10.5% among women. On the other hand, the DH model presented the least accurate estimates. Thus, as it was hypothesized, for longer-term predictions, the performance of the risk factors' model was better that that of simpler methods. When performing predictions to 2020, the risk factors' model yielded estimates of an increase in the number of cases of 6.0% among men and 9.7% among women, while the naive model estimated increases of 10.7% and 16.1%, respectively, and the DH model estimated increases of 20.2% and 3.2%.

Table 3. Comparison of the prediction models for the year 2010 in Northern Portugal.

		Men	Women
Cases observed	2000	135	34
	2010	186	38
Cases predicted for 2010	Naive model (n)	197	48
	DH model	229	69
	n (95% confidence interval)	(146-311)	(21-117)
	Risk factors' model	188	42
	n (95% credibility interval)	(177-203)	(37-45)
% deviation from observed cases in 2010	Naive model	5.9	26.3
	DH model	23.1	81.6
	Risk factors' model	1.1	10.5

DH: Dyba and Hakulinen methods

The major strengths of the model proposed in this thesis were the incorporation of detailed information on the exposure to the different risk factors, the separate assessment of esophageal cancer by subtype to incorporate the knowledge on the etiology of the disease and the evaluation of esophageal cancer as a multifactorial disease. These should be regarded as important steps towards a proper evaluation of the burden of disease related to this cancer.

It will be necessary to define the appropriate balance between the complexity of the model, namely regarding the number of risk factors and the type of exposure information to be used, and the accuracy of the predictions needed for planning of interventions and to define cancer control policies.

CONCLUSIONS

A marked increase in esophageal cancer incidence was observed in Western countries over the last decades. In Europe, increasing EAC incidence trends were observed in most countries, while ESCC rates have been decreasing or stabilizing over the last few decades. Nordic countries and the UK registered the steepest increases in EAC trends among men, and EAC is now the predominant histological type in those settings. In central and southern Europe, smaller rises in EAC were observed and ESCC remains the predominant subtype among men. Among European women, ESCC remained the predominant subtype and rates increased in some countries.

Numerous systematic reviews and meta-analyses have been published regarding the association between esophageal cancer's major risk factors and its occurrence. For some risk factors, the strength of association with esophageal cancer varied notoriously between histological types (e.g., tobacco smoking), and for others the association was only found significant for one of the subtypes (e.g., alcohol consumption).

In most settings, the prevalence of tobacco smoking has been decreasing among men and increasing among women, and mean BMI has been found increasing for both sexes. The prevalence of alcohol consumption and the mean daily intake of fruit, vegetables and red meat presented heterogeneous patterns across countries and between sexes. The prevalence of *H. pylori* infection decreased worldwide, although different rates of improvement were observed between countries.

A model aiming to describe and predict the trends in esophageal cancer incidence, taking into account the changes in the exposures to risk factors, showed that the trends were mainly influenced by changes in fruit and red meat intake, and body mass index, although differences were observed across countries with different patterns of variation of incidence rates. In Northern Portugal, predictions using the proposed model yielded closer values to the ones observed than other methods. This thesis adds to previous research on this topic a framework for analysis of the contribution of the variation in the exposure to different factors known to be associated with esophageal cancer, as well as for long-term predictions of ESCC and EAC at a population level. The results obtained in this work show the potential of this model for the planning of interventions and to define cancer control policies, but future studies, performing longer-term predictions, while also using more accurate estimates of the variation in the exposure to the risk factors, are expected to improve the accuracy of predictions.

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